

## SCD FINGERPRINTS

The present invention relates to the use of cluster of differentiation (CD) molecules in detecting the presence and/or assessing the progression and/or assessing the response to therapeutic intervention of one or more disease states in an individual. In particular  
5 it relates to the use of profiles/fingerprint/s of shed CD (sCD) molecules in body fluids in detecting and/or assessing the progression of one or more disease states in an individual. Further uses of sCD profiles according to the present invention are also described.

10 Background to the invention

Rapid and accurate diagnosis is essential in medicine as in many cases early diagnosis and successful treatment correlates with a better outcome and reduced hospitalisation. Currently, the clinical diagnosis and staging of many diseases of global significance  
15 involve different invasive procedures such as histopathological analysis of biopsy samples which are usually obtained when the disease process is at a relatively advanced stage. In many cases, a classic histopathological approach may not be sufficient to produce accurate diagnosis and any delay in confirming the diagnosis would have financial and morbidity repercussions for the healthcare institution and  
20 most importantly for the individual. Disease states and disease staging are also determined by different imaging techniques such as X-rays, nuclear magnetic resonance (NMR), CT analysis and others, however, these are expensive and impractical when dealing with large numbers of individuals, or when it is necessary to monitor disease progression closely, or in health institutes or clinical situations where  
25 such equipment is unavailable. Furthermore such investigations are impractical for individuals because it would result in such individuals obtaining high radiation doses. For this reason such tests cannot be carried out serially and are thus of little use in monitoring drug responses and monitoring disease progression.

30 A variety of diseases or the predisposition to such a disease can be characterised by changes in the overall patterns and/or expression levels of various genes and their

proteins. For example, some cancers are associated with changes in the expression of oncogenes or tumour suppressor genes. Furthermore, disease conditions or disorders associated with dysregulated cell cycle and development can be attributed to changes in transcriptional regulation of specific genes.

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Although there are several genetic assays available to assess gene mutations, the identification of specific genetic changes may not always be a direct indicator of a disease or disorder and thus cannot be relied upon as an accurate prognostic indicator.

10 Certain genetic changes are exhibited by alterations in cell surface antigens. Again, however, prior attempts to develop a diagnostic assay for complex disease conditions or disorders based on the identification of single antigen or very small numbers of antigens have not been uniformly successful.

15 In addition, or alternatively, biochemical analysis of a patient may be used to diagnose a disease state. For example, the presence of Bence Jones proteins in urine is an indicator that an individual has multiple myeloma. However, classical biochemical methods are limited, for example an elevated cholesterol in serum indicates hypercholesterolaemia but does not definitively indicate atherosclerosis. A further  
20 disadvantage of biochemical methods of diagnosis is that they generally permit the measurement of only one or two indicator/s of disease in any one test. Consequently, they provide an incomplete picture of the disease state of an individual. Moreover, if several tests are performed in an attempt to provide a more complete picture, this inevitably increases the number of variables which complicates interpretation.  
25 Furthermore, for many diseases there are no reliable biochemical markers, especially for diseases of global importance such as breast cancer, colorectal cancer and lung cancer. In the case of solid tumours such as colorectal cancer, a number of carcinoembryonic antigen (CEA) markers have been identified, however they have poor sensitivity and very low specificity. The situation is similar with disease  
30 conditions requiring surgical intervention. There is still, for example, no marker for acute appendicitis and consequently, a great many patients undergo unnecessary invasive surgery. It has been estimated that more than 40,000 unnecessary appendicitis

operations occur each year due to misdiagnosis with associated costs of \$700 million. In a recent larger retrospective study, Flume and colleagues show that misdiagnosis occurs in 15% of instances.

- 5 Therefore, there is a pressing need in the art to provide a simple and complete picture of the disease state or condition of an individual. Such a 'picture' would be of use in predicting and/or detecting the presence of a disease or condition, in assessing the therapeutic strategies and the potential of various agents and in monitoring the progression and successful treatment of disease states or conditions

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- Lymphocytes and other leukocytes express a large number of different antigens associated with their outer plasma membranes that can be used to identify distinct functional cell subsets. Many of these antigens were "classically" known to be receptors for growth factors, cell-cell interactions, viruses eg CD4, CD 112 and CD  
15 155 are the HIV, poliovirus receptor 2 and poliovirus receptor respectively), and immunoglobulins; molecules for cell adhesion or complement stimulation; enzymes and ion channels. A single systematic nomenclature has been adopted to classify monoclonal antibodies to human leukocyte cell surface antigens termed cluster of differentiation (CD) antigens, also referred to as CD molecules/antigens (Kishimoto *et al.*, 1996 Proceedings of the Sixth International Workshop and Conference held in  
20 Kobe, Japan. 10-14 Garland Publishing Inc, NY, USA). This work originated as the direct result of the work of one of the inventors (Dr. César Milstein) of the present application who invented monoclonal antibody technology with his colleague Georges Kohler (Kohler and Milstein. Continuous cultures of fused cells secreting antibody of defined specificity (1975), Nature Aug 7, 256 (5517), 495-7) and who identified and  
25 raised the first monoclonal antibodies to both non-human and human CD antigens (McMichael *et al.* A human thymocyte antigen defined by a hybrid myeloma monoclonal antibody).

- 30 The data required in order to define a CD has changed over the years, not surprisingly in view of the advances in modern technology. Initially, clustering depended absolutely on the statistical revelation of similarities in reaction pattern of two or more

antibodies, analysed on multiple tissues. It is now accepted that CD molecules may also be classified by molecular characteristics. Thus it has become customary to use the CD marker (for example CD21) to indicate the molecule recognised by each group of monoclonal antibodies. The current list of CD markers is constantly updated as new  
5 antigens are identified and eventually, the CD list will encompass all human lymphocyte cell surface antigens and their homologues in other mammalian and non-mammalian species (Mason *et al.*, 2001, *Immunology*, 103, 401-406). It should be noted that although CD antigens were initially defined in the basis that they are expressed on the cell surface of leukocytes, a great many of them are also expressed on  
10 numerous other cell types including brain, liver, kidney, red blood cells, bone marrow, dendritic antigen presenting cells, epithelial cells, stem cells, thymocytes, osteoclasts, NK cells, B cells, macrophages, to name but a few.

Historically, CD cell surface antigens have been used as markers in diagnosis. Indeed  
15 leukemias are diagnosed on the basis of cell morphology, expression of specific CD antigens, lymphoid (LY) and myeloid (MY) antigens, enzyme activities and cytogenetic abnormalities such as chromosome translocations. The expression of up to three CD antigens on leukemia cells is determined using labelled antibodies to particular CD antigens with analysis by flow cytometry.

20 Significantly, however, it has been observed that often (if not always in normal or disease states) the surface bound CD immunological specificity molecules (intact CD molecules or fragments thereof) are found soluble in the serum and in other body fluids. Subsequent research has shown that indeed CD molecules can be secreted from  
25 cells as a result of "active" processes such as alternative splicing (Woolfson and Milstein, PNAS, 91 (14) 6683-6687 (1994)) or "passive" processes such as cell surface shedding. Thus, CD molecules can be found in three forms, membrane associated CD molecules, shed CD molecules (sCD) produced by alternative splicing or other mechanisms and intracellular CD molecules. Each of these can be complete molecules  
30 or fragments thereof.

It is generally accepted however that the change in levels of any one sCD is not specific to a given disease state and cannot therefore usefully be used in the diagnosis of disease states.

5 Recent studies (those of WO 00/39580) have described a system for the diagnosis of haematological malignancies, whereby immunoglobulins are immobilised on a solid support and are used to detect cell-surface antigen levels, in particular cell-surface CD antigen levels in samples of cells. Using this approach, a pattern of expression of cell-surface bound CD antigens is generated which the inventors have shown to be  
10 indicative of the presence of various defined leukemias in a patient. However, there are several disadvantages with this technique. Firstly and importantly, it is a cell-based technique. Such techniques have many disadvantages associated with them, for example that of background noise and the difficulty of measuring antigen levels accurately. Such methods only allow semiquantitative determination of the relative  
15 densities of sub-populations of cells of distinct immunophenotypes, indeed absolute quantification using this method may not be possible. Another problem with this prior art method is that at equilibrium, the number of cells captured by the immobilised antibody dot depends not only on the affinities of the interactions, the concentration of the antibody dot, the level of expression of the CD antigen on the cell surface and in  
20 addition to this the stereochemical availability and accessibility of the monoclonal antibody immobilised on the nitrocellulose membrane of the CD antibody array. Furthermore computerised quantification of the cell density as indicated by the pixel intensity corresponding to each dot of arrayed antibody, depends not only on the number of cells in the test sample, but in addition to the cell size and morphology. In  
25 addition to all of these factors, the absolute requirement for purification of cells from whole blood and the possible need to fractionate blood cells still further makes such an approach both labour intensive and time consuming.

Therefore, there still exists a need in the art for a simple method for diagnosis of  
30 different diseases and conditions by the measurement of CD antigens wherein such method produces a complete, sensitive, specific and accurate picture of disease.

**Summary of the invention**

The present inventors have surprisingly found that particular disease states can be characterised by specific patterns of levels of shed/soluble/secreted (sCD) (as herein  
5 defined) CD molecules derived from the body fluids of an individual. That is, the profile or 'sCD print' of the levels of sCD antigens correlate with particular diseases or disorders or physiological states such as those induced by administration of a drug or toxin. This finding is especially surprising since the levels of sCDs found in the body fluids of an individual are generally very low, and the sCD released by cells would  
10 only be expected to change in some, and not all cell types of an individual when affected by one or more diseases, the change of levels of shed CD levels, as herein defined detectable in the body fluids of diseased individuals as compared with non-diseased individuals would be expected to be minimal.

15 Thus, in a first aspect, the present invention provides a shed CD (sCD) fingerprint (sCD print) of one or more disease states.

In the context of the present invention, the term 'CD' refers to a different cell surface leukocyte molecule recognised by a given monoclonal or group of monoclonal  
20 antibodies which specifically 'cluster' to the antigen/molecule in question. Many, if not all of these molecules produce forms which are released from the cell surface by alternative splicing, proteolytic cleavage, dissociation or other mechanisms. Thus in the context of the present invention, the term 'shed CD molecule (sCD)' is synonymous with the term secreted/soluble CD (sCD) and refers to a released form of  
25 a cell surface leukocyte molecule in which at least a portion of that molecule is recognised by a given monoclonal or group of monoclonal antibodies as herein described. It should be noted however, that the antibody used to recognise the CD molecule may not be monoclonal. It may be engineered, an artificial construct consisting of an expressed fragment derived from an antibody molecule with intact  
30 recognition, or it may be a non-protein molecular recognition agent, or a protein recognition agent which is not an antibody, or is an antibody hydrid, for example made by introducing antibody binding sites into a different scaffolding. Advantageously, as

herein defined a shed form of sCD is generated by various mechanisms including but not limited to any of those selected from the group consisting of the following: alternative splicing, proteolytic cleavage and dissociation.

5 In the context of the present invention it is important to note that the CD nomenclature is a simple method for representing a whole range of molecules. For example: CD14 is the lipopolysaccharide receptor, LP5-R; CD21 is the EBV receptor; CD 25 is the IL-2Ralpha receptor; CD 31 is PECAM-1; CD 44 is H-CAM; CD 50 is ICAM-3; CD 54 ICAM-1; CD 62E is LECAM-2; CD 62L is LECAM-1; CD 86 is B 70; CD 95 is FAS  
10 apoptosis antigen; CD 102 is ICAM-2; CD 106 is VCAM-1; CD 116 is GM-CSFR alpha; CD 117 is c-kit stem cell factor receptor; CD 124 is IL-4R alpha; CD 126 is IL-6Ralpha; CD 130 is gp 130; CD 138 is syndican-1; CD 141 is thrombomodulin; CD 91 is low density lipoprotein receptor-related antigen; CD 132 is common cytokine receptor gamma), CD 89 is IgA Fc receptor, CD 74 is class II specific chaperone, CD  
15 95 is apoptosis antigen; CD220 is the insulin receptor and CD 184 is the chemokine receptor 4. (CXCR4) CD8 is Lin 2; CD 27 is low affinity IgE-R; CD 30 is Ki-1.

The present inventors realised that sCDs act as representatives/ambassadors for the families of molecules from which they are shed. Thus sCD 184 stands as an  
20 ambassador for all shed (as defined herein) cell surface chemokine receptors and for example sCD54 acts as an ambassador for all intercellular adhesion molecules. Furthermore they realised that cell behaviour can be interrelated on the basis of the patterns of sCD molecules shed by cells.

25 In this regard it should be noted, as mentioned above that sCDs are ambassadors for a vast range of molecules including but not limited to the following: integrins, adhesion molecules, Fc receptors, apoptosis antigens, blood group antigens, viral receptors, coagulation factors, selectins, chemokine receptors, macrophage receptors, insulin receptors, prion proteins, glycoporphins, rhesus antigens, T cell receptor zeta chain and  
30 pregnancy specific antigens.

As herein defined, the term 'shed CD fingerprint (sCD)' describes the pattern or profile of levels of more than one shed CDs in one or more individuals. A sCD fingerprint as herein defined may be representative of one or more non-diseased individual/s or one or more diseased individual/s. Preferably, a shed CD fingerprint describes the level of five or more shed CD molecules, more preferably it is 6, 7, 8, 9, 10 or more sCD molecules, more preferably still a shed CD fingerprint describes the levels of 15 or more sCD molecules. More preferably a shed CD fingerprint describes the levels of 20 or more sCD molecules. Most preferably, it comprises the levels of sCDs for the complete set of sCDs for a given individual.

sCD levels from normal and/or diseased individuals may be collated in order to generate one or more reference sCD fingerprints. A 'reference' sCD fingerprint (sCD print) is a fingerprint which is advantageously generated from sCD measurements from more than one individual and is representative of the sCD levels of either a 'normal' or diseased individual. Advantageously, these reference fingerprints are collected together to form a database so that abnormal fingerprints generated from patient samples can be distinguished from normal reference fingerprints in the database. In addition, by comparing one or more patient sample fingerprints with one or more reference fingerprint/s corresponding to one or more diseases, then the disease state of an individual may be established.

A shed CD (sCD) fingerprint (sCDprint) may be generated from one individual. Preferably however, each fingerprint is generated from more than one individual. Advantageously, it is generated from more than five, ten, fifteen or twenty, 50, 100, 500, 1000, 5000, 10,000, 50,000 or 100,000 individuals. One skilled in the art will appreciate that the greater the number of individuals used to generate the reference fingerprint, then the more representative of any given disease state or of a normal individual the reference sCD profile/s will be. Fingerprints may be simplified by using the average values of the data obtained for each sCD for a number of individuals. For example, the modal value is used for data obtained from a very small number of samples. Such information may then be placed within a database as herein described.

One skilled will appreciate that often more than one disease state may be present in an individual at a given time. This may complicate the CD fingerprint obtained, such that the fingerprint is an aggregate fingerprint of several disease states. The effect of multiple disease states (composites) in an individual may be minimised if the reference  
5 fingerprint for any given disease state is generated from several or many individuals. Importantly, composites may generate their own patterns and be used as reference in their own right.

Measuring the levels of sCD molecules is carried out using methods known to one  
10 skilled in the art and described herein.

sCD levels are measured in samples of body fluids. Suitable body fluids for measuring sCDs include any one or more selected from the group consisting of the following: tissue fluid, serum, blood, cerebrospinal fluid, synovial fluid, urine, plural fluid, saliva,  
15 lymphatic fluid, aspirate, bone marrow aspirate and mucus. One skilled in the art will appreciate that this list is not intended to be exhaustive.

In a further aspect the present invention provides a method of generating a shed CD (sCD) fingerprint of one or more disease state/s comprising the step of measuring in  
20 parallel the levels of more than one shed CD in one or more samples from one or more individuals and collating the data.

According to the above aspect of the invention, the term 'measuring in paralell' (sCD levels) refers to the process where sCD levels are measured in one or more samples  
25 taken from an individual at substantially the same time. Those skilled will appreciate that in the case where sCD levels are measured from more than one body fluid sample, then it may not be practical to take more than one sample of body fluid from the same individual at precisely the same time. Thus according to the above aspect of the invention, when more than one body fluid sample is to be taken from an individual for  
30 the generation of a sCDprint, then such samples should be taken from the same individual as close together in time as possible. Advantageously, the term 'close together' (in time) means within 5 hrs of one another, more advantageously within 4

hrs, 3hrs, 2 hrs, 1 hr, 30 mins, 20 mins, 10 mins, 5 mins, 1 min of one another. Those skilled will appreciate that so long as there is no change in levels of measured sCDs between the first sample and the last sample being taken, then such a time interval can be considered 'close together' as described herein. Thus so long as there is no change  
5 in sCD levels between the first sample and the last sample being taken, then such samples can be considered to be taken 'in paralell' and likewise such sCD levels can be considered to be measured 'in paralell' as referred to herein.

According to the above aspect of the invention, the samples for testing are used to  
10 generate a given sCD profile/fingerprint/pattern/barcode (sCDprint) and may be from one body fluid type or more than one body fluid type. Advantageously the one or more samples for testing and used to generate a sCD profile are taken from more than one body fluid for any given disease state. Advantageously, a number of sCD levels are measured from the same body fluid sample. More advantageously, all of the sCD  
15 levels comprising a fingerprint are measured in paralell from one body fluid sample.

As used herein, the term 'collating' the data means to put the data into a form so that one or more pattern/s of the levels of sCDs within that disease state is apparent. Advantageously, the data will be entered into a database as described herein. More  
20 advantageously, the database is an integrated database as described herein, comprising clinical data linked to specific sCD fingerprint patterns/profiles.

As the present inventors surprisingly found that a sCD fingerprint/profile (sCDprint) of a diseased individual is different from that of a non-diseased individual, it was realised  
25 that by comparing the sCD fingerprint/profile (sCDprint) of a sample from a diseased patient with that of one or more reference sCD fingerprints representing one or more defined disease states then the presence and nature of a disease in that individual could be ascertained.

30 Thus, in a further aspect, the present invention provides a method for predicting the presence of one or more disease states in an individual comprising the step of

comparing one or more sCD fingerprint/s (sCDprint/s) generated from that individual with one or more reference sCD fingerprint/s.

5 In the context of the present invention, the term 'predicting the presence of one or more disease states' refers to the process of detecting the presence of one or more disease states before the onset of the clinical signs of the disease are apparent in the individual. The clinical signs of disease are characteristic of each disease state or group of disease states, as long as the disease is present in that individual.

10 As referred to herein, the comparing step may refer to comparing an individuals sCD fingerprint/profile (sCDprint) with one or more reference sCD fingerprint/s of one or more disease state/s and/or with a reference sCD fingerprint of a non-diseased 'normal' individual.

15 In a further aspect still, the present invention provides a method for detecting the presence of one or more disease states in an individual comprising the step of comparing one or more sCD fingerprint/s generated from that individual with one or more reference sCD fingerprint/s.

20 The term 'detecting the presence of one or more disease states' refers to the detection of the presence of one or more disease states in an individual once the clinical signs of one or more disease states are apparent in that individual. In addition, the term refers to the process of detecting the presence of one or more disease states in an individual other than the disease state whose clinical signs are apparent in that individual.

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According to the above two aspects of the invention, the reference sCD fingerprint/s may be from non-diseased (normal) individuals and/or from diseased individuals. Alternatively, or in addition the reference sCD fingerprints/profiles may be derived from normal subjects who have undergone some form of intervention. Such  
30 interventions include but are not limited to treatment with chemotherapeutic or other agents, exposure to radiation and exposure to pathogens. Those skilled in the art will be aware of other interventions as used herein. According to the above two aspects of

the invention, preferably, the sCD fingerprint/s/profiles (sCDprint) are from diseased individuals.

5 In a further aspect still, the present invention provides a method for detecting the extent of one or more disease states in an individual comprising the step of comparing one or more sCD fingerprint/s generated from that individual with one or more reference sCD fingerprint/s.

10 As referred to above, the term 'detecting the extent of one or more disease states' includes within its scope detecting the severity of one or more disease states within an individual. For example it may allow low grade and high grade forms of the disease to be distinguished. It allows localised and metastasised forms of a particular disease to be distinguished. In such cases one or more sCD fingerprints of an individual are compared with one or more reference disease sCD fingerprints representative of  
15 disease states at one or more degrees of severity. For example, in the case of neoplastic disease the presence or absence of metastasis may be detected using the method of the present invention.

20 In a further aspect, the present invention provides a method for assessing the progression of a disease state in an individual comprising the step of comparing the sCD fingerprint of an individual at two or more periods during the occurrence of the disease.

25 In the context of the present invention, the term 'assessing the progression of a disease state' means assessing whether the disease has increased in severity, decreased in severity or remains the same severity compared with a different period during the life-span of the disease. In addition the term 'assessing the progression of a disease state' includes within its scope monitoring the progression of a disease state.

30 The term 'period' in the context of the present invention, generally refers to a time period.

As defined herein, the term a 'disease state' refers to any impairment of the normal physiological functions affecting an organism or any disease condition, disorder or the presence of a particular microbial, viral, parasitic or other pathogenic agent known to one skilled in the art. Suitable disease states for analysis as described herein include  
5 but are not limited to: infectious, neoplastic, autoimmune, immunological, metabolic, degenerative, psychological, psychiatric, iatrogenic, inflammatory, drug or toxin related, vascular, traumatic and endocrine diseases. Advantageously, 'a disease state' as herein defined refers to any one or more disease selected from the group which includes but is not limited to: infections such as bacterial, fungal, protozoan, parasitic,  
10 prion and viral infections, non-neoplastic disorders; stroke; heart condition; atherosclerosis; pain; diabetes, obesity; anorexia; bulimia; asthma; Parkinson's disease; thrombosis; acute heart failure; hypotension; hypertension; urinary retention; metabolic bone diseases such as osteoporosis and osteopetrosis; angina pectoris; hepatitis; myocardial infarction; ulcers; asthma; allergies; rheumatoid arthritis;  
15 inflammatory bowel disease; irritable bowel syndrome benign prostatic hypertrophy; pancreatitis; chronic renal failure and psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome and others. Most preferably it refers to appendicitis; Bence Jones  
20 Proteinuria; Chronic Myeloid Leukemia; Colorectal cancer; chronic renal failure; Crohn's Disease; Diabetic Nephropathy; Cardiac pathology; Infection; Liver damage; Lymphoma; macrocytic anaemia; Prostate Cancer; Oligoclonal Banding and Pulmonary Embolism/Deep Vein Thrombosis (eg DVT/PE). One skilled in the art will appreciate that this list is not intended to be exhaustive. Indeed this method should be  
25 suitable for most if not all diseases.

Examples of shed cluster of differentiation molecules suitable for measurement to generate a sCD fingerprint for use in the methods of the present invention include but are not limited to CD14, CD25, CD31, CD44, CD50, CD54, CD62E, CD62L, CD86,  
30 CD95, CD106, CD116, CD124, CD138, CD141, CD40L, CD8, CD23, CD30, CD40. Those skilled in the art will be aware of other suitable sCD molecules for analyses according to the methods of the present invention. They will also be aware of other

members of the family that each sCD stands as an ambassador for, such as chemokine receptors, interleukin receptors and inter-cellular adhesion molecules.

Measuring CD levels may be carried out using methods known to those skilled in the art and described herein. Shed CD (sCD) levels may suitably be measured in samples of tissue fluids which include, but are not limited to: serum, plasma, lymph fluid, pleural fluid, synovial fluid, follicular fluid, seminal fluid, amniotic fluid, milk, whole blood, urine, cerebrospinal fluid (CSF), ascites, saliva, sputum, tears, perspiration, and mucus. Advantageously, sCD levels are measured from samples of serum using reagents suitable for detecting shed CDs that include but are not limited to antibodies raised against those CDs. Preferably monoclonal antibodies or engineered antibodies, including phage antibodies raised against shed CDs or their membrane bound forms are used for their detection. However non-protein agents may also in principle be used to detect sCD molecules. Similarly the detecting molecule may contain antibody bonding site fragments incorporated into the scaffold of another molecules or an engineered scaffold. Commercially available kits for measuring CD levels include those from Diaclone 1, Bd A Fleming BP 1985 F-25020 Besancon Cedex-France and Medsystems Diagnostics GmbH, Rennweg 95b, A-1030 Vienna Austria.

Suitable techniques for measuring levels of sCDs include but are not limited to immunoassay including ELISA using commercially available kits such as those described above, flow cytometry particularly multiplexed particle flow cytometry as herein described. Those skilled in the art will be aware of other suitable techniques for measuring CD levels in samples from an individual including antibody 'chip' array type technologies or chip technologies utilizing non-classical antibody binding site grafted molecules. Suitable techniques for measuring levels of sCDs are described in more detail in the detailed description of the invention.

Shed CD levels are also measured in a number of individuals with one or more disease states as herein defined, such as appendicitis and the like. Generally one or more shed CDs levels will be elevated in a given disease state as compared with the range found in normal individuals. However, some sCD levels decrease in some disease states

compared with the range found in 'normal' individuals and such decreases may also form part of a sCD fingerprint of the present invention. Thus, by measuring the ranges of levels of various shed CDs found in a number of individuals with one or more defined disease state/s a 'fingerprint' of shed CD levels for any defined one or more diseases is generated. Likewise by measuring the ranges of levels of various shed CDs found in a number of individuals who have undergone one or more interventions (such as chemotherapeutic treatment, exposure to pathogens, exposure to radiation, individuals who have undergone a given vaccination program etc) then a 'fingerprint' (sCDprint) of shed CD levels for a given intervention may be generated. Those skilled in the art will appreciate that a sCD fingerprint (sCDprint) representative of an intervention may be generated from diseased or non-diseased individuals.

Preferably, the sCD fingerprint of an individual is generated from any two or more sCDs selected from the group consisting of the following: CD14, CD25, CD31, CD44, CD50, CD54, CD62E, CD62L, CD86, CD95, CD106, CD116, CD124, CD138, CD141, CD40L, CD8, CD23, CD30, CD40. One skilled in the art will appreciate that this list is not intended to be exhaustive and may include CD homologues of human and other mammalian or non-mammalian species. One skilled in the art will appreciate though that in general animal reference sCD fingerprints cannot be used to analyse human diseases and *vice-versa*. For instance sCD patterns/profiles/fingerprints could be defined in the rat or mouse using rat or mouse equivalent CD monoclonal antibodies as herein described. This would be an invaluable adjunct for studying these animal model systems, especially in the area of therapeutics, gene knockouts and other such proteomic and genomic studies.

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The invention can also be used for testing human and other mammalian and non-mammalian species using sCD fingerprints from the appropriate animal.

One skilled in the art will appreciate that the methods of the present aspect of the invention can be used to test potential therapeutic agents suitable for the prophylaxis and/or treatment of diseases. An agent of therapeutic potential will affect the sCD profile or 'fingerprint' of the disease: If several fingerprints are taken at various stages

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of a disease and compared with those obtained from samples in which an individual has been treated with a potential therapeutic agent, then the effect on one or more sCD fingerprints can readily be assessed.

- 5 In addition, the method of the present invention may also be used to monitor patient compliance with taking a particular drug (agent), and/or undergoing a particular treatment regime.

Thus, in a further aspect still, the present invention provides a method for assessing the  
10 effect of one or more agent/s on one or more disease states in an individual comprising the step of comparing a sCD fingerprint of an individual at two or more different time periods.

According to the above aspect of the invention, preferably the agent is a potentially  
15 therapeutic agent.

In the context of the present invention the term to 'assess the effect' means to detect any changes in the severity or other characteristics of any one or more diseases in an individual. Such changes will be reflected in a change in sCD profile/fingerprint of an  
20 individual.

Preferably the agent is a potentially therapeutic agent. The term 'potentially therapeutic agent' means any agent that may cause a beneficial effect on an individual suffering from one or more diseases. Such beneficial effects may be for example  
25 reducing the clinical signs of the one or more diseases. It is an important feature of the present invention though, that a change in level of any one sCD in isolation is not always indicative of a change in severity of a disease. It will be appreciated though that in some cases, a change in the level of one sCD in isolation will be indicative of a change in severity of a disease.

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Generally, individual sCD levels will be elevated in a disease state as compared with a 'normal' non-diseased individual. Occasionally however, the level of an individual

sCD will decrease in a disease state as compared with a normal non-diseased individual. However, according to the present invention, it is the changes of the profile of a number of sCDs (that is a fingerprint) during a disease which provides an accurate measure of the effect of one or more agents on a disease state in an individual.

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One skilled in the art will appreciate that on occasion a selection of the complete repertoire of sCDs available for testing may be measured. The selection chosen may vary according to the disease state being tested.

10 According to this aspect of the invention, sCDs suitable for generating a sCD fingerprint are as described herein.

Therapeutic agents may be tested for their effect on any one or more disease states selected from the group consisting of the following: infections, autoimmune disease,  
15 neoplastic, vascular endocrinological, metabolic, inflammatory degenerative, psychiatric psychological, traumatic, drug/toxin-related, bacterial, fungal, protozoan and viral infections, non-neoplastic disorders; pain; diabetes, obesity; anorexia; bulimia; asthma; pregnancy; endocrine; vascular; metabolic; gastro-intestinal; iatrogenic; psychiatric; psychological; exercise-induced; diet-related; ME;  
20 degenerative; Parkinson's disease; thrombosis; atherosclerosis; acute heart failure; hypotension; hypertension; erectile dysfunction; urinary retention; metabolic bone diseases such as osteoporosis; angina pectoris; hepatitis; myocardial infarction; ulcers; allergies; rheumatoid arthritis; inflammatory bowel disease; irritable bowel syndrome benign prostatic hypertrophy; psychosis; psychiatric disorders; including anxiety;  
25 schizophrenia; manic depression; delirium; dementia; severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome; and preferably tumours which can be benign or malignant cancers; breast cancer; myeloma; melanoma; bladder cancer; leukaemia; plasmocytoma and others, but most preferably appendicitis; Bence Jones Proteinuria; Chronic Myeloid Leukaemia;  
30 Colorectal cancer; chronic renal failure; Crohn's Disease; Diabetic Nephropathy; Cardiac pathology; Infection; Liver damage; Lymphoma; macrocytic anaemia; Prostate Cancer; Oligoclonal Banding and PE/DVT

Suitable agents for assessment according to the method of the present invention may be naturally occurring or synthetic. Naturally occurring agents include proteins, peptides or nucleic acids. They may be agents known to be of therapeutic value or they  
5 may be of unknown therapeutic value.

In a further aspect, the present invention provides a method for sub-categorising a sCD fingerprint profile comprising the steps of identifying within one or more disease states one or more sub-group/s of sCDs wherein each sub-group of sCDs exhibits common  
10 characteristics distinguishing it from any other sub-group within that disease category.

As used herein the term a 'sCD sub-category' describes a sub-group of sCDs which show a defined fingerprint/profile (sub-fingerprint) of sCD levels within a larger fingerprint of one or more disease states wherein each sub-group of sCDs exhibits  
15 common characteristics distinguishing it from any other sub-group within those one or more disease states.

In a further aspect still, the present invention provides a sCD reference database comprising pathological and/or normal sCD fingerprint patterns.  
20

As herein described the term 'a reference database' refers to a collection of sCD fingerprints from normal 'non-diseased' and/or diseased individuals. Advantageously, the database is computer generated and/or stored. Advantageously the data from more than 5 individuals is present in the database. More advantageously the data from more  
25 than 10, 100, or 1000 individuals comprises the database. More advantageously still the data from more than 10,000 or more than 50,000 individuals comprises the database. Most advantageously the data from more than 100,000 individuals comprises the database. Advantageously the database, in addition to sCD data will also comprise clinical information relating to various patients and/or disease conditions.  
30 Alternatively or in addition, a database according to the present invention comprises genomic information such as mRNA expression profiles, and/or sCD body fluid profiling data, and/or CD cell surface pattern data, and/or clinical data. Most

advantageously, the database will be in the form of an integrated clinical database comprising accurate patient details including co-morbidity, age, sex, smoking status etc.

- 5 Recent studies which have investigated the impaired expression of NKG2D and T-cell activation by tumour-derived soluble MHC ligands (Nature, vol 419, 17 October 2002). Studies have shown that tumours release large amounts of the MHC class I homologue MIC into the serum. Activation of the NKG2D receptor on natural T cells is known to stimulate their ability to destroy tumours, but the high levels of tumour  
10 derived MIC seem to downregulate the NKG2D receptor and block the antitumour effect. (Nature, vol 419, 17<sup>th</sup> October 2002, p679, pg 734). These soluble forms of MHC are produced either by enzymatic cleavage or by alternative splicing (Nature, vol 419, 17<sup>th</sup> October 2002, p679, pg 734).
- 15 It is apparent from the present disclosure that sCDs may be produced by alternative splicing (Woelfson and Milstein, PNAS Vol 91, pp 6683-6687), enzymatic cleavage or other mechanisms and that such shed forms are associated with disease (Sugiyama et al., Non-invasive detection of bladder cancer by identification of abnormal CD44 proteins in exfoliated cancer cells in urine, Journal of Clinical pathology, 48, 3, 142-  
20 147; Yoshida, K et al, Abnormal retention of intron 9 in CD44 transcripts in human gastrointestinal tumours. Cancer research 55, 4273-4277). The present inventors consider that sCD molecules may also bind to a ligand/receptor and thereby block down stream effects. Thus, the present inventors have realised that the blockage of the production of sCD molecules via the inhibition of any of the methods of sCD  
25 generation described herein, may be a therapeutically useful method for the prophylaxis or treatment of one or more diseases or disorders including but not limited to any of those in the group consisting of infections, inflammation, vascular, iatrogenic, endocrine, drug-related disorders, toxin related disorders, and cancer in particular metastasis and leukemia.

Thus in a further aspect still, the present invention provides a method for treating one or more diseases comprising the step of inhibiting the production of one or more sCDs within an individual.

- 5 In a further aspect still, the present invention provides the use of an inhibitor of the production of one or more sCDs in the preparation of a medicament for the treatment of disease.

According to the above aspect of the invention, the term 'an inhibitor of the production  
10 of one or more sCDs' refers to one or more agents which inhibit the production of a shed form of sCD as herein defined. Advantageously, the inhibitor is a specific inhibitor of those one or more sCDs. Suitable inhibitors include alternative splicing inhibitors and/or enzymatic cleavage inhibitors. Advantageously, the inhibitor is an alternative splicing inhibitor. Such alternative splicing inhibitors include for example  
15 inhibitors of exonic splicing enhancers (Fairbrother et al, Science, vol 297, 9<sup>th</sup> August 2002).

According to the above aspects of the invention, the production of any one or more sCDs present in the body fluid of an individual may be inhibited. Advantageously, the  
20 one or more sCDs are any one of those selected from the group consisting of the following: CD14, CD25, CD31, CD44, CD50, CD54, CD62E, CD62L, CD86, CD95, CD106, CD116, CD124, CD138, CD141, CD40L, CD8, CD23, CD30, CD40. More advantageously the sCD is CD1. Advantageously, the sCD is CD1 and the inhibitory agent is an alternative splicing inhibitor and/or a gene specific CD1 inhibitor.

25

It should be noted that the present inventors consider that the invention described herein can be used to post hoc re-analyse clinical trial data, assigning patients to different sub-groups for analysis on the basis of their sCDprints and in doing so potentially revealing previously unseen statistical effects and at the same time  
30 identifying responders or non-responders to a therapeutic intervention, and those who respond adversely to the intervention in the case in which a therapeutic agent has not been taken further due to adverse responses in small numbers of individuals.

## Definitions

5

The term '**CD**' refers to a different cell surface leukocyte molecule recognised by a given monoclonal or group of monoclonal antibodies which specifically 'cluster' to the antigen/molecule in question. Many, if not all of these molecules produce forms which are released from the cell surface by alternative splicing, proteolytic cleavage, dissociation or other mechanisms.

10

Thus in the context of the present invention, the term '**shed CD molecule (sCD)**' refers to a released form of a cell surface leukocyte molecule in which at least a portion of that molecule is recognised by a given monoclonal or group of monoclonal antibodies as herein described. Advantageously, as herein defined a shed form of sCD is generated by various mechanisms including but not limited to any of those selected from the group consisting of the following: alternative splicing, proteolytic cleavage and dissociation.

15

As herein defined, the term '**shed CD fingerprint/profile (sCD)**' or '**sCDprint**' describes the pattern or profile of levels of more than one shed CD measured in one or more body fluids from one or more individuals. A sCD fingerprint as herein defined may be representative of one or more non-diseased individual or a one or more diseased individual/s. Preferably, a shed CD fingerprint describes the level of five or more shed CD molecules, more preferably it is 6, 7, 8, 9, 10 or more sCD molecules, more preferably still a shed CD fingerprint describes the levels of 15 or more sCD molecules. Most preferably a shed CD fingerprint describes the levels of 20 or more sCD molecules.

20

25

As used herein the term a '**sCD sub-category**' describes a sub-group of sCDs which show a defined fingerprint/profile (**sub-fingerprint**) of sCD levels within a larger fingerprint of one or more disease states wherein each sub-group of sCDs exhibits

30

common characteristics distinguishing it from any other sub-group within those one or more disease states.

As defined herein, the term a '**disease state**' refers to any impairment of the normal physiological functions affecting an organism or any disease condition, disorder or the presence of a particular microbial, viral, parasitic or other pathogenic agent known to one skilled in the art. Suitable disease states for analysis as described herein include but are not limited to: infectious, neoplastic, autoimmune, immunological, metabolic, degenerative, psychological, psychiatric, iatrogenic, inflammatory, drug or toxin related, vascular, traumatic and endocrine diseases. Advantageously, 'a disease state' as herein defined refers to any one or more disease selected from the group which includes but is not limited to: infections such as bacterial, fungal, protozoan, parasitic, prion, and viral infections, non-neoplastic disorders; stroke; heart condition; atherosclerosis; pain; diabetes, obesity; anorexia; bulimia; asthma; Parkinson's disease; thrombosis; acute heart failure; hypotension; hypertension; urinary retention; metabolic bone diseases such as osteoporosis and osteopetrosis; angina pectoris; hepatitis; myocardial infarction; ulcers; asthma; allergies; rheumatoid arthritis; inflammatory bowel disease; irritable bowel syndrome benign prostatic hypertrophy; pancreatitis; chronic renal failure and psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome and others. Most preferably it refers to appendicitis; Bence Jones Proteinuria; Chronic Myeloid Leukemia; Colorectal cancer; chronic renal failure; Crohn's Disease; Diabetic Nephropathy; Cardiac pathology; Infection; Liver damage; Lymphoma; macrocytic anaemia; Prostate Cancer; Oligoclonal Banding (myaesthenis gravis) and Pulmonary Embolism/Deep Vein Thrombosis (eg DVT/PE). One skilled in the art will appreciate that this list is not intended to be exhaustive.

Examples of shed cluster of differentiation molecules suitable for measurement to generate a sCD fingerprint for use in the methods of the present invention include but are not limited to CD14, CD25, CD31, CD44, CD50, CD54, CD62E, CD62L, CD86, CD95, CD106, CD116, CD124, CD138, CD141, CD40L, CD8, CD23, CD30, CD40.

Those skilled in the art will be aware of other suitable sCD molecules for analyses according to the methods of the present invention.

As defined herein the term 'an antibody' includes within its scope for example IgG, IgM, IgA, IgD or IgE) or fragment (such as a FAb, F(Ab')<sub>2</sub>, Fv, disulphide linked Fv, scFv, diabody) whether derived from any species naturally producing an antibody, or created by engineered DNA technology (for example fluorobodies, green fluorescently labelled antibodies); whether isolated from serum, B-cells, hybridomas, transfectomas, yeast or bacteria). It also includes within its scope, non-protein binding agents which  
10 comprise the binding specificity of an antibody molecule, or a binding capacity in general for a determinant or sub-determinant of a component of the protein structure/glycoprotein structure of a CD molecule.

#### Brief description of the figures

15

**Figure 1. Disease Groups. Multiples of upper limit of normal (ULN). All sCD's included**

The limits indicated by each point are:

- No shading  $\leq 1 \times \text{ULN}$
- 20 • Lightly shaded  $1 - 2 \times \text{ULN}$
- Darkly shaded  $> 2 \times \text{ULN}$
- A white slash in the box indicates no data available.

**Figure 2.** All sCD's that appear not to discriminate from the normals (sCD's 21; 102; 117, 126; 130; 26; 44v5; 44v6; 62P).  
25

**Figure 3.** Disease Groups. Mode of Response for Remaining 20 sCD's.  
To simplify the data further the modal response for each disease group was plotted.

**Figure 4.** Disease Groups. Mode of Response for remaining sCD's.  
30 Data has been ranked in order of increased expression.

**Figure 5.** Disease Groups. Mode of Response for remaining sCD's.

**Figure 6.** Disease Groups. Mode of Response for all sCD's.

As for Figure 3 (except all sCD's are included).

5 The limits indicated by each point are:

- No shading  $\leq 1 \times \text{ULN}$
- Lightly shaded  $1-2 \times \text{ULN}$
- Darkly shaded  $> 2 \times \text{ULN}$

A white slash in the box indicates no data available.

10 **Figure 7.** Disease Groups. Mode of Response for all sCD's.

**Figure 8.** Disease Groups. Mode of Response for all sCD's.

**Figure 9.** Shows the patterns of levels of sCDs during various infectious disease states as compared with a group of 'normal' non-diseased individuals.

15 **Key:** Lightly shaded box-sCD levels unchanged  
Darkly shaded box-sCD levels increased  
Shaded box with diagonal line-sCD levels decreased.

20 **Figure 10.** Shows the patterns of levels of sCDs during various inflammatory/autoimmune diseases as compared with a group of 'normal' non-diseased individuals.

**Key:** Lightly shaded box-sCD levels unchanged  
Darkly shaded box-sCD levels increased  
25 Shaded box with diagonal line-sCD levels ~~decreased~~

**Figure 11.** Shows the patterns of levels of sCDs during various 'other diseases' as compared with a group of 'normal' non-diseased individuals.

**Key:** Lightly shaded box-sCD levels unchanged  
30 Darkly shaded box-sCD levels increased

Shaded box with diagonal line-sCD levels decreased

**Figure 12.** Shows the patterns of levels of sCDs during various neoplastic disease states as compared with a group of 'normal' non-diseased individuals.

5

**Key:** Lightly shaded box-sCD levels unchanged  
Darkly shaded box-sCD levels increased  
Shaded box with diagonal line-sCD levels decreased

**Figure 13.** Shows the patterns of levels of sCDs during various cardiovascular diseases as compared with a group of 'normal' non-diseased individuals.

10

**Key:** Lightly shaded box-sCD levels unchanged  
Darkly shaded box-sCD levels increased  
Shaded box with diagonal line-sCD levels decreased

15

**Figure 14.** Shows the patterns of levels of sCDs during various metabolic and haematological diseases as compared with a group of 'normal' non-diseased individuals.

20

**Key:** Lightly shaded box-sCD levels unchanged  
Darkly shaded box-sCD levels increased  
Shaded box with diagonal line-sCD levels decreased

25

**Figure 15.** Shows the patterns of levels of sCDs during various haematological malignancies as compared with a group of 'normal' non-diseased individuals.

**Key:** Lightly shaded box-sCD levels unchanged  
Darkly shaded box-sCD levels increased  
Shaded box with diagonal line-sCD levels decreased

30 **Detailed description of the Invention**

**General techniques**

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art (e.g., in cell culture, molecular genetics, nucleic acid chemistry, hybridisation techniques and biochemistry). Standard techniques are used for molecular, genetic and biochemical methods (see generally, Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 2d ed. (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. and Ausubel *et al.*, Short Protocols in Molecular Biology (1999) 4<sup>th</sup> Ed, John Wiley & Sons, Inc. which are incorporated herein by reference) and chemical methods. In addition Harlow & Lane., A Laboratory Manual Cold Spring Harbor, N.Y, is referred to for standard Immunological Techniques.

### *sCD molecules according to the invention*

In a first aspect, the present invention provides a shed CD (sCD) fingerprint (sCD print) of one or more disease states.

In the context of the present invention, the term 'CD' refers to a different cell surface leukocyte molecule recognised by a given monoclonal or group of monoclonal antibodies which specifically 'cluster' to the antigen/molecule in question. Many, if not all of these molecules produce forms which are released from the cell surface by alternative splicing, proteolytic cleavage, dissociation or other mechanisms.

Thus in the context of the present invention, the term 'shed CD molecule (sCD)' refers to a released form of a cell surface leukocyte molecule in which at least a portion of that molecule recognised by a given monoclonal or group of monoclonal antibodies as herein described.

### **Location of sCD molecules.**

Although first identified on leukocytes. CD antigens have been located on other blood cells and non-blood cells. CD molecules have been found on many different blood cell types including the following blood cell types: erythroid, dendritic cells, B cells, pre-B

cells, T cells (cytotoxic, suppressor and helper subtypes), monocytes, myeloid cells, endothelial cells, platelets, NK cells (natural killer cells), red blood cells, thymocytes. Those skilled in the art will appreciate that this list is not intended to be exhaustive.

5 In addition, CD antigens have been found on the following non-immune cells myocytes, peripheral nerve, liver, platelet precursors, lung cells, cerebellum, cortex, glia, neuroepithelium, placenta, prostate, spinal cord, brain, muscle, kidney, salivary glands, muscle, melanoms, leukemias, lymphoma, hematopoietic cells, lymphoid progenitor cells, breast, astrocytes, thyroid, lung, pancreas, trachea, schwann cells, 10 trophoblast, erthroblast, microglia.

In the context of the present invention it is important to note that the CD nomenclature is a simple method for representing a whole range of molecules. For example: CD14 is the lipopolysaccharide receptor, LP5-R; CD21 is the EBV receptor; CD 25 is the IL- 15 2Ralpha receptor; CD 31 is PECAM-1; CD 44 is H-CAM; CD 50 is ICAM-3; CD 54 ICAM-1; CD 62E is LECAM-2; CD 62L is LECAM-1; CD 86 is B 70; CD 95 is FAS apoptosis antigen; CD 102 is ICAM-2; CD 106 is VCAM-1; CD 116 is GM-CSFR alpha; CD 117 is c-kit stem cell factor receptor; CD 124 is IL-4R alpha; CD 126 is IL- 6Ralpha; CD 130 is gp 130; CD 138 is syndican-1; CD 141 is thrombomodulin; CD8 20 is Lin 2; CD 27 is low affinity IgE-R; Cd 30 is Ki-1;

The present inventors realised that sCDs act as representatives/ambassadors for the molecules from which they are shed. Furthermore they realised that cell behaviour can be interrogated on the basis of the patterns of sCD molecules shed by cells.

## 25 **Generation of a fingerprint of one or more disease states**

In a first aspect, the present invention provides a shed CD (sCD) fingerprint of one or more disease states.

Clinical signs and symptoms and various biochemical indicators of disease are used to 30 identify individuals with one or more defined disease states. sCD levels are then measured for a number of sCDs present in one or more body fluid samples from each individual, preferably in a number of individuals using methods known to those skilled

in the art and described herein, in order to generate a reference disease state or reference composite disease state fingerprint for those one or more given disease states.

5    (A) Diagnosis of disease states

      i. Diagnostic Indicators Used.

Appendicitis

- 10                   – Request for Amylase at admission A&E/MAU Subsequent  
                      Histopathological Diagnosis

Bence Jones Proteinuria

- 15                   – Multiple myeloma in which the malignant plasma cells excrete only  
                      light chains of one type (either 2 or 3); lytic bone lesions occur in  
                      about 60% of the cases, and light chains (Bence Jones protein) can be  
                      detected in the urine  
                      – Positive finding

Chronic Myeloid Leukaemia

- 20                   – Histopathological Diagnosis

Colorectal Carcinoma

- Histopathological Diagnosis

25    Chronic Renal Failure

- Prolonged elevation of serum creatinine.

Crohn's Disease

- Histopathological diagnosis

30

Diabetic Nephropathy

- Identified by abnormal urine Albumin/Creatinine ratio from subjects

attending diabetic clinic.

#### Cardiac Pathology

- MI (as diagnosed by increased CK, symptoms and ECG changes).

5

#### Infection

CRP (C reactive protein) > 250 g/l (e.g. *Staphylococcus aureus* infections).

10

#### Liver Damage

- Clinical Details Alcoholic Liver Disease/Poisoning. Abnormal liver function tests.

15 Lymphoma

- Histopathological Diagnosis

#### Macrocytic Anaemia

- Diagnosed by haematological parameters. Hb <10 g/dL; MCV > 100 fL

20

#### Oligoclonal Banding

- small discrete bands in the gamma globulin region of the spinal fluid electrophoresis, indicating local central nervous system production of IgG; bands are frequently seen in patients with multiple sclerosis but can also be found in other diseases of the central nervous system including syphilis, sarcoidosis, and chronic infection or inflammation.

25

30 VQ (pulmonary angiogram)

#### Pulmonary Embolism/Deep Vein Thrombosis

- ultrasound VQ or CT pulmonary angiogram scan (ventilation perfusion mismatch)

#### Prostate Carcinoma

- 5                   – Histopathological diagnosis and elevated PSA.

In general, a combination of the patient's history, medical examination, general health and indicators provided from biochemical, histochemical, radiochemical and other types of tests and disease and/or clinical signs of disease will be used in the diagnosis  
10 of disease. For the avoidance of doubt, the term 'clinical signs and symptoms of disease' means the same as 'clinical details' of disease.

#### (B) Samples of body fluids from disease states

For each sCD the following information is generally obtained a) the dynamic range of  
15 the assay b) the range of concentrations expected in health c) the range of concentrations expected in disease. From this information an approximate dilution factor for each assay may be obtained, allowing maximum use of subject samples. One skilled will appreciate thought that in some circumstances body fluid samples may not be diluted for testing.

20 Suitable body fluids for measuring sCD levels as herein defined include whole blood, serum, urine, tissue fluid, cerebrospinal fluid, lymphatic fluid, synovial fluid, aspirate, bone marrow aspirate, mucus or other tissue or body fluid. One skilled in the art will appreciate that this list is not intended to be exhaustive. Preferably sCD levels are  
25 measured in serum which is prepared from whole blood using methods familiar to those skilled in the art At least 1.5ml of sample is required for testing of all the sCDs. Advantageously, less than 1.5 mls of sample is required for such testing. More advantageously, much smaller volumes of sample will be needed for such testing. In addition, the present inventors have shown that haemolysis and lipaemia can interfere  
30 with some immunoassays used for detecting sCDs and therefore samples are used which exhibit minimal haemolysis and lipaemia.

Body fluid samples may be diluted in order to measure the sCD levels and the dilution factor for each sCD should be the same for the generation of the fingerprints for all disease states tested. One skilled in the art will appreciate that the dilution factor may be adjusted in order to focus on either high or low concentrations of sCDs.

5 Advantageously, the dilution factor will be adjusted to focus on high concentrations of sCDs.

(C) Methods of measuring sCD levels.

Suitable methods for measuring levels of sCDs in body fluids include flow cytometry, in particular multiplexed particle flow cytometry, immunoassay and microarray  
10 technologies utilising antibody or ligand interactions. Advantageously, sCDs levels are measured using multiplexed particle flow cytometry and/or chip based monoclonal antibody technology, engineered antibody molecules or non-antibody or non-protein molecules that recognise sCD antigens. These methods will be familiar to those skilled  
15 in the art.

(i) Immunoassays

Immunoassays such as immunoblotting (detecting membrane-bound and soluble proteins), and enzyme linked immunoassays (ELISA) provide a sensitive and specific  
20 means of detecting target substances.

Although the various types of immunoassays are performed differently, they have one thing in common-they all involve antibodies. Used in an appropriate immunoassay system, specificity leads to sensitivity. As herein defined the term 'antibodies' includes  
25 antibody fragments, engineered immunoglobulin folds or scaffolds which have a binding affinity for soluble CD molecules.

One skilled in the art will appreciate that the 'immunoassay technique' may be adapted to use other molecules which selectively bind sCDs. Those skilled in the art will be  
30 aware of such molecules.

In a direct immunoassay, the antibody used as the primary reagent is advantageously given a fluorescent, enzymatic, or radio-active detection means. In indirect immunoassays, the secondary antibody-usually polyclonal antisera produced by a goat or a rabbit against human immunoglobulins-carries the detection means. When a  
5 secondary antibody is used, the initial immune reaction between the primary antibody and the target antigen is amplified, producing a more readily detectable signal.

Western blots of electrophoretically separated proteins (immunoblots), on the other hand, are generally probed with antibodies labeled with an enzyme or a radioisotope  
10 such as  $^{125}\text{I}$ . Chromogenic or chemiluminescent substrates can also be used. For example, enzymes such as HRP and AP catalyze chromagenic reactions, in which a colourless substrate is converted into a coloured compound, and also chemiluminescent reactions where light is emitted.

15 Chromogenic substrate kits are commercially available and include but are not limited to for example alkaline phosphatase, horseradish peroxidase, and TMB peroxidase (TMB is tetramethylbenzidine, the substrate in this case). Boehringer Mannheim also has several enzyme substrates for immunoassays available. They include but are not limited to for example ABTS (2,2+-azino-di-3-ethylbenzthiazoline sulfonate) and  
20 TMB (tetramethylbenzidine), which are used with HRP; and 4-nitrophenyl phosphate and 5-bromo-4-chloro- 3-indolyl phosphate (BCIP) for immunoassays in which an alkaline phosphatase-conjugated antibody is used.

Chemiluminescent substrates are available from companies such as Pierce, which for  
25 example, produces the SuperSignal CL-HRP Substrate, an enhanced chemiluminescent substrate for horseradish peroxidase. This system detects specific proteins on immunoblots with a sensitivity that rivals radioactivity (reportedly to picogram levels). When the chemiluminescent substrate is applied to membrane-bound proteins on an immunoblot, an instantaneous but long-lasting flash of light is produced.

30

Commercially available immunoassay kits for measuring sCD levels include those from Diaclone 1, Bd A. Fleming BP 1985 F-25020 Besancon Cedex-France which

provides kits for the measurement of a number of CD molecules including CD 14, CD21, CD25, CD31, CD44, CD50, CD54, CD62E, CD62L, CD86, CD95, CD102, CD106, CD116, CD117, CD124, CD126, CD130, CD138, CD141, CD40L. Medsystems diagnostics GmbH, Rennweg 95b, A-1030 Vienna Austria, also provides  
5 kits which measure sCD levels.

(ii) Flow cytometry

Techniques for carrying out flow cytometry are familiar to those skilled in the art and are described in Flow Cytometry: A Practical Approach. Edited by MG Ormerod. IRL  
10 Press, Oxford. 1994. ISBN 0-19 963461-0. Practical Flow Cytometry. 3rd Edition. Howard M Shapiro. Alan R Liss, Inc. ISBN 0-471-30376-3. Flow Cytometry. First Principles. Alice Longobardi Givan. Wiley-Liss, New York, 1992. ISBN 0-471-56095-2. Handbook of Flow Cytometry Methods. Edited by J Paul Robinson. Wiley-Liss, New York, 1993. ISBN 0-471-59634-5.

15

(iii) Multiplexed particle flow cytometry assay

Methods for simultaneously assaying different proteins in individual samples are commercially available. Some of those commercially available are detailed below:

20 The versatile laboratory multianalyte profiling (LabMAP™) system developed by Luminex Corp. of Austin, Texas, can be used for virtually any bioassay that is based on the specific binding of one molecule to another, for example a monoclonal antibody raised against a sCD and a CD molecule.

25 LabMAP assays for a sCD molecule can be based on the immunological detection, and/or may follow the gain or loss of fluorescence (e.g., when a mAb raised against a sCD binds to a sCD target). LabMAP assays employ three different fluorochromes: two to create color-coded microspheres, and the third for quantifying the reaction. Polystyrene microspheres are internally dyed with precise ratios of two spectrally  
30 distinct fluorochromes. This ratio confers a unique identifying "signature" or "spectral address" to each microsphere set.

Bioassays are conducted on the surfaces of the microspheres. Each capture probe (e.g., sCD-specific antibody or other affirmative detection reagent) is immobilized onto a color-coded set of microspheres using any of a variety of different surface chemistries. Luminex offers microspheres bearing Lumavidin™ (an avidin derivative),  
5 for immobilizing biotinylated molecules, or carboxyl groups, for covalently coupling protein. The binding of analyte to an immobilized probe is detected via a detection reagent labeled with the third fluorochrome. Luminex currently offers 100 different microsphere sets, each of which can be used for the simultaneous measurement of a different analyte. Thus, in theory, up to 100 different species can be simultaneously  
10 measured in a single tube or microplate well.

The Luminex microsphere product line is designed specifically to work with the instruments available from Luminex or their partners. The Luminex 100™ instrument uses microfluidics to align the microspheres in single file and employs two lasers,  
15 one for the detection of the fluorescent microsphere itself, and the other for the reporter reagent. The colour signals are captured by an optics system and translated into binding data via digital signal processing.

Instrumentation, reagents, and custom services for LabMAP technology users are  
20 also available from companies other than Luminex. For example, Bio-Rad Laboratories of Hercules, Calif., introduced the Bio-Plex™ Protein Array System. This system combines a fluorescent reader with the software, protocols, and supplies needed for performing LabMAP-based assays in a 96-well microplate format. The primary benefits of the Bio-Plex Protein Array System, other than up  
25 to a 100-fold increase in data, include significantly reduced sample requirements.

The Cytometric Bead Array (CBA) system from BD Biosciences of San Diego is flexible in that it accommodates multiple sizes and fluorescent intensities of particles. The system includes everything the researcher needs to implement this technology,  
30 including a cytometer setup kit with the requisite software, reagents and standards. The company's CBA assay kits employ their proprietary bead sets, which are internally dyed with varying intensities of a proprietary fluorophore. These sets are

distinguished via one fluorescence parameter and two size discriminators. However, the system is also capable of handling assays based on the use of other types of spectrally distinct microsphere sets. The CBA analysis software is an "add-in" for Microsoft Excel®, and is compatible with contemporary data acquisition software  
5 such as CellQuest™. Researchers can employ a variety of preset configurations for generating standard dilution series and calibration curves, and data reports can be generated at each step in the process.

(iv) "Antibody Chip" array technology.

10

The array format has revolutionised biomedical experimentation and diagnostics, enabling ordered high-throughput analysis. During the past decade, classic solid phase substrates, such as microtitre plates, membrane filters and microscopic slides, have been turned into high-density, chip-like structures.

15

Protein array technology allows high throughput screening for gene expression and molecular interactions. Protein arrays appear as new and versatile tools in functional genomics, enabling the translation of gene expression patterns of normal and diseased tissues into protein product. Protein function, such as enzyme activity, antibody  
20 specificity, and other ligand-receptor interactions and binding of nucleic acids or small molecules can be analysed on a whole genome level.

As the array technology develops, an ever increasing variety of formats become available (eg nanoplates, patterned arrays, three-dimensional pads, flat-surface spot  
25 arrays, microfluidic chips), and proteins can be arrayed onto different surfaces (e.g, membrane filters, polystyrene film, glass, silane, gold). Various techniques are being developed for producing arrays. The emerging future array systems will be used for high-throughput functional annotation of gene products.

30 Protein microarrays are particularly useful in molecular diagnostics The concept of the array library was central to this development which now extends from DNA to protein. Similar to the gene chip arrays measuring mRNA levels on a genome wide scale, the

protein product of expressed cells can be used for the simultaneous assessment of protein levels on a proteome wide scale. Additionally, protein specific antibodies can be arrayed to produce "antibody chip arrays" (Cahill D., 2001, *J. Imm. Meth.* **250**, 81-91). The availability of such antibody chip arrays can be used to simultaneously  
5 analyse numerous interactions within a single sample. The "antibody chip" can be used to demonstrate antibody-protein interactions by incubating the chip with target proteins which have been labelled with a traceable marker (ProteinChip, CIPHERGEN Biosystems, Fremont, CA, USA; BIAcore chips, Biacore, Upsala, Sweden) or by incubating the chip with protein molecules or fragments thereof and detecting  
10 association between antibody and protein molecule or fragment thereof using ELISA type assays (Caliper Technologies, Mountain View, CA, USA; Orchid Biocomputer Inc., Princeton, NJ, USA). It should be noted that sCDs according to the invention may be found complexed with a ligand and thus chip based technology described herein may be used to measure/demonstrate interactions of ligand bound sCD with other  
15 molecules.

Techniques for preparing antibody arrays are described below:

The antibodies may be covalently linked to a suitable membrane such  
20 as an Immobilon P membrane (PVDF; Millipore Corporation) Subsequent blocking with an excess of a protein solution such as a skim milk preparation is preferred. A blocking agent is designed to eliminate non-specific binding on the binding surface Other suitable blocking agents are Irish moss extract or other source of carrageenan or gelatin. The antibodies are also adsorbed to a nitrocellulose film on a glass microscope  
25 slide (Schleicher and Schuell, NH, USA) and the unbound nitrocellulose is then blocked with skim milk. Antibodies are also adsorbed to Nylon membranes. To increase the accessibility of bound anti- CD antibodies to antigens on cells, the solid support used for the array is initially coated with a recombinant, truncated form of Protein G from *Streptococcus* which retains its affinity for the Fc portion of IgG  
30 lacks albumin and Fab binding sites, and membrane-binding regions (Goward et al., 1990). Antibodies are applied to this coat of Protein G and bind via their domains leaving the Fab domains free to interact with cells. The Fab domains are also further

from the solid support providing greater accessibility of CD antigens on cell membranes to antibodies.

The array of antibodies is also constructed on a membrane or a coverslip. In this case,  
5 the antibodies are covalently linked to the membrane as duplicate spots in a two dimensional matrix. The spots are arranged in a matrix such as but not limited to a 15x 15 matrix.

The antibodies are advantageously monoclonal and are specific for the cluster of  
10 differentiation (cluster designation) antigens (CD antigens). Details of CD antigens are available at [http://www.ncbi.nlm.nih.gov/prow/cd/index\\_molecule.htm](http://www.ncbi.nlm.nih.gov/prow/cd/index_molecule.htm). The spots are of microscopic size and are produced by the application of a drop (~ 10 nanolitres) of antibody solution (e.g. 10<sup>6</sup> tg protein/ml) on designated portions of a membrane or glass surface such as a coverslip, first washed with a non-specific protein absorbent  
15 such as 30% w/v skim milk (Dutch Jug, Bonlac Foods Ltd, Melbourne, Australia) and then rinsed. Other protein solutions and other brands of skim milk may also be employed. The antibodies may be covalently coupled to the solid support such as through amino groups of lysine residues, the carboxylate groups of aspartate or glutamic acid residues or the sulphydryl groups of cysteine residues. The array of  
20 antibodies selectively binds cells from body fluids which express the respective antigens or may bind free antigens. A positive and/or negative control is included such as an antibody for surface molecules or soluble molecules known to be present in the sample. An example of one form of the assay device is shown in Fig. 3. The solid support is conveniently of similar size and shape to a microscope slide and may be  
25 constructed of glass or other polymeric material.

A wall around the microscope slide may be separately added or moulded with the slide and this facilitates retention of fluid material. The present invention extends to any other device capable of fulfilling the method of the present invention.

30

In the case of nitrocellulose based antibody arrays are preferably constructed using a Biodot Aspirate and Dispense System (Cartesian Technologies) where 5 nL dots are

applied to a nitrocellulose film. on glass microscope slides (Schleicher and Schuell, Cat. No. 10484182). Purified monoclonal antibodies (Beckman Coulter, Becton Dickinson or Biosource International) are used at concentrations recommended for flow cytometric analysis and are applied in the same buffers as supplied by the  
5 manufacturers. The nitrocellulose is then blocked by incubation with 5 % w/v skim milk (Dutch Jug) for 1.5 h at 37°C. These blocking conditions are chosen to minimize background binding.

The stability of the arrays is further enhanced by adding protein stabilizing agents to  
10 the antibodies (e.g. polyethylene glycol or stabilizer products commercially available from Surmodics, MN, USA).

The following description provides a preferred method for preparing the antibody arrays: The panel of antibodies is generally used to construct antibody arrays with the  
15 Cartesian Technologies PixSys™ 3200 Aspirate and Dispense System. The antibodies are chosen for use in a particular diagnosis or detection protocol. Each antibody is generally applied in the volume of from about 1 to about 10 nanoliters in a dot format at approximately from 0.5 to 1.5 min intervals to create an appropriate array on a nitrocellulose film generally laid on a solid support such as but not limited to a  
20 microscope slide, plastic or gold support. After dotting, the supports are assessed on a light box and the corners of the arrays marked gently using, for example, a lead pencil. The antibody arrays are then immersed in a blocking agent such as but not limited to skim milk, Irish moss extract or other source of carrageenan or gelatin. From about 2 % to about 15 % w/v skim milk powder in PBS at 4°C overnight or at 37°C for from  
25 about 60-120 minutes is particularly useful. After application of the blocking agent, the solid supports are washed gently with purified water and allowed to dry at room temperature for a period of time from about 60-120 minutes.

The solid supports are then stored in an airtight bag at 4°C in the dark  
30

An alternative method of detection is the use of acoustic detection based methods, such as those described by Akubio Technology. (DDT vol 7, No 5 (Suppl.) 2002). This

form of detection technology is based on the sound made as molecular interactions are disrupted. It does not use any form of electromagnetic radiation. Very high accelerations, millions of times the force of gravity are used to disrupt such interactions. Such forces are generated by an acoustic wave device such as a quartz crystal resonator. By monitoring the change in resonant frequency of the crystal ,  
5 which occurs on adsorption of mass to the surface, quartz crystal resonators can be used together with appropriate surface chemistry and fluidics to detect the adsorption of proteins, oligonucleotides, cells and other particles to surface-bound receptors. This allows the label-free determination of interaction affinities and kinetics in real time.  
10 (Janshoff A et al (2000) Piezoelectric mass-sensing devices as biosensors. An alternative to optical biosensors. Angew. Chem, 39, 4004-4032); Ward et al, (1990) In situ interfacial mass detection with piezoelectric transducers, Science 249, 1000-1007).

(D) A sCD fingerprint for one or more disease states according to the present invention  
15 Advantageously, levels of sCDs are measured in diseased individuals and absolute values may be divided by the upper limit of normal (ULN) obtained from healthy individuals. The data is collated and the resultant pattern of values obtained for each sCD for one or more given disease states, from one or more individuals forms the basis of a sCD fingerprint of one or more given disease states.

20 The statistical significance of the increases or decreases in sCD levels found in various disease states can be assessed using a number of methods.

The sCD fingerprint can advantageously be simplified by removing those sCDs whose  
25 levels do not generally change significantly during one or more given disease states. Examples of such sCDs include but are not limited to CD21, CD102, CD117, CD 126, CD130, CD 26, CD44v5, CDv6, CD62P. For example see Figure 2.

To simplify the fingerprint further, instead of showing the data from each individual  
30 for any given sCD during a disease, a modal value for each sCD calculated from the group of individuals may be plotted. The rationale of this is demonstrated in Figures 3, 5, 6, 7, 8. This provides an easily readable and simple 'fingerprint' of a disease.

One skilled in the art will appreciate that there are many methods suitable for the statistical analysis of the sCD level data measured as herein described. These include but are not limited to cluster analysis and other statistical methods for the detection of patterns.

### **Statistical analysis**

Methods for the statistical analysis of data are known to those skilled in the art. An example of a suitable protocol for the analysis of data is outlined below:

(i) The statistical analysis procedures described here relate to immunoprecipitation assays of soluble CD molecules in samples arrayed in 96-well microtitre trays.

Statistical analysis of the proposed antibody-chip arrays could essentially follow the same procedures, although modifications would inevitably need to be made to account for experimental design and data quality issues specific to that technology.

In the present analysis, each tray was designed to measure the concentration of a specific soluble CD molecule in a number of samples. Trays were prepared for each of 29 soluble CD molecules, for each of three sets of 37 patients. In all, the three sets of patients represented 17 disparate disease groups, including one group of healthy individuals. The 96 wells on each tray contained: sera from each of the 37 patients of one set (duplicated); a standard control preparation containing the target antigen at each of 7 different concentrations (duplicated); pooled sera from 'normal' control patients (replicated 3 times); and the same pooled sera spiked with the target antigen (replicated 3 times).

Each tray was washed with a solution containing fluorescently labelled monoclonal antibody specific to its designated target antigen, and exposed to light. For each well, a measurement of light absorption was recorded.

(ii) *Statistical analysis using artificial intelligence type neural networking*

This method describes the ability of the computer system which analyses the data to learn to recognise patterns in data. Thus the more the system is used, the better able the system is to recognise patterns. Such a system is described in amongst other documents Sven Olsson et al (2002), Clin Physiol & Func Im (2002) 22, pp295-299; Sijo Perekattil et al (March 2003), Journal of Virology, vol 169, pg 917-920. This approach is reviewed in PJG Lisboa, (2002), Neural Networks 15, 11-39. All of these documents are herein incorporated by reference.

*Data preparation*

The recorded light absorptions were mathematically transformed, as follows.

- ⑩ Absorptions were converted to antigen concentrations, via a calibration curve based on the absorptions recorded for the antigen standards in the same tray. Absorptions of dubious quality were flagged *missing*, and omitted from subsequent analysis.
- ⑩ Concentrations exceeding that of the most concentrated antigen standard of the tray were flagged as *high*. Concentrations corresponding to absorptions at the limit of instrumentation were similarly flagged.
- ⑩ Each flagged concentration was replaced by the concentration of its duplicate in the tray, provided the duplicate concentration was not also flagged.
- ⑩ The average of each concentration with its duplicate was computed. We refer to these as *mean concentrations*.
- ⑩ For each CD, the 10th and 90th centiles of the distribution of mean concentrations in normal individuals was computed. We refer to these as  $CD_{10}$  and  $CD_{90}$ . Subtracting  $CD_{10}$  from  $CD_{90}$  gives a range, which we denote  $CD_{range}$ . *Concentration categories* were defined for each CD as follows:

⑩

Category	from	to
-1	0	CD <sub>10</sub>
0	CD <sub>10</sub>	CD <sub>90</sub>
1	CD <sub>90</sub>	CD <sub>90</sub> + CD <sub>range</sub>
2	CD <sub>90</sub> + CD <sub>range</sub>	CD <sub>90</sub> + 2 x CD <sub>range</sub>
3	CD <sub>90</sub> + 2 x CD <sub>range</sub>	CD <sub>90</sub> + 3 x CD <sub>range</sub>
4	CD <sub>90</sub> + 3 x CD <sub>range</sub>	-

⑩ To control for differences in the scale of reactivity of different CDs, to stabilise variability between duplicates across the range of concentrations, and to relate concentrations to values obtained for normal individuals, each mean concentration was put into the appropriate concentration category of its CD. All concentrations flagged *high* were put into the highest category. We refer to these as *categorised concentrations*.

⑩

### *Data analyses*

10

### *Cluster analysis*

A cluster analysis was performed to identify clusters of CDs having similar patterns of reactivity across the patients, standards and controls. Likewise, a second cluster analysis was performed to identify clusters of patients with similar profiles of reactivity across the CDs. Cluster analyses were hierarchical and based on the categorised concentrations, described above, using a Euclidean distance metric and the average linkage criterion for cluster merging.

20 The results from the cluster analyses were displayed in the form of a level plot, a part of which is given in **figure 16**. In this level plot, the rows correspond to CDs and the columns correspond to patients, standards and controls. Rows and columns are ordered so that those in the same cluster are adjacent. Also, dendrograms were produced showing the hierarchy of clusters, separately for the clustering of CDs and for the clustering of patients, standards and controls. Each cell in the level plot is toned to

25

indicate its categorised concentration, deep blue corresponding to Category -1 (below normal), and deep red corresponding to Category 4 (high). Missing concentrations are denoted by an 'X'.

5 *A sCD fingerprint database according to the invention*

In a further aspect still, the present invention provides a sCD reference database comprising pathological and/or normal sCD fingerprint patterns.

10 As herein described the term 'a database' refers to a collection of sCD fingerprints from normal 'non-diseased' and/or diseased individuals. Advantageously, the database is computer generated and/or stored. Advantageously the data from more than 5 individuals is present in the database. More advantageously the data from more than 10, 100, or 1000 individuals comprises the database. More advantageously still the  
15 data from more than 10,000 or more than 50,000 individuals comprises the database. Most advantageously the data from more than 100,000 individuals comprises the database.

Advantageously the database, in addition to sCD data also comprises clinical  
20 information relating to various patients and/or disease conditions. Alternatively or in addition, a database according to the present invention comprises genomic information and/or sCD profiles relating to specific disease states and other pathological states and clinical data. Thus the inventors contemplate the use of a database in which sCD data and other data may be integrated and used to obtain a more complete analysis of one or  
25 more disease states.

*Uses of one or more 'fingerprints of disease' according to the present invention*

30 In a further aspect, the present invention provides a method for predicting the presence of one or more disease states in an individual comprising the step of analysing the sCD fingerprint in that individual.

In a further aspect still, the present invention provides a method for detecting the presence of one or more disease states in an individual comprising the step of analysing the pattern/s of shed CD levels of more than one shed CD which is present  
5 in that individual.

In a further aspect still, the present invention provides a method for detecting the extent of one or more disease states in an individual comprising the step of comparing one or more sCD fingerprint/s generated from that individual with one or more  
10 reference sCD fingerprint/s.

In yet a further aspect, the present invention provides a method for assessing the progression of a disease state in an individual comprising the step of comparing the sCD fingerprint of an individual at two or more periods during the occurrence of the  
15 disease.

In a further aspect still, the present invention provides a method for assessing the effect of one or more agent/s on one or more disease states in an individual comprising the step of comparing a sCD fingerprint of an individual at two or more time periods.  
20

In a further aspect, the data generated by the present invention is used to compile a reference database, comprising pathological and/or normal sCD fingerprints, against which the expression sCD pattern of any individual will be compared.

25 In a further aspect still, the present invention provides the use of a sCD fingerprint to assess the effect of one or more agents in an individual.

An embodiment of the present invention is its use as a tool for assessing the affect different diet and exercise regimes may have on human or other mammals.  
30

Additionally, the present invention may be used to construct sub-categories of sCD fingerprint profiles, suitable for common therapeutic treatment.

*The therapeutic inhibition of the production of one or more sCDs according to the invention*

5 Recent studies which have investigated the impaired expression of NKG2D and T-cell activation by tumour-derived soluble MHC ligands (Nature, vol 419, 17 October 2002). Studies have shown that tumours release large amounts of the MHC class I homologue MIC into the serum. Activation of the NKG2D receptor on noatural T cells is known to stimulate their ability to destroy tumours, but the high levels of tumour  
10 derived MIC seem to downregulate the NKG2D receptor and block the antitumour effect. (Nature, vol 419, 17<sup>th</sup> October 2002, p679, pg 734). These soluble forms of MHC are produced either enzymatic cleavage or by alternative splicing (Nature, vol 419, 17<sup>th</sup> October 2002, p679, pg 734).

15 It is apparent from the invention described herein that sCDs may be produced by alternative splicing (Woelfson and Milstein, PNAS Vol 91, pp 6683-6687), enzymatic cleavage or other mechanisms. The present inventors consider that sCD molecules may also bind to a ligand/receptor and thereby block down stream effects. Thus, the present inventors have realised that the blockage of the production of sCD molecules  
20 via the inhibition of any of the methods of sCD generation described herein, may be a therapeutically useful method for the prophylaxis or treatment of one or more diseases in particular tumourigenesis.

Thus in a further aspect still, the present invention provides a method for treating one  
25 or more diseases comprising the step of inhibiting the production of one or more sCDs within an individual.

In a further aspect still, the present invention provides the use of an inhibitor of the production of one or more sCDs in the preparation of a medicament for the treatment  
30 of disease.

According to the above aspect of the invention, the term 'an inhibitor of the production of one or more sCDs' refers to one or more agents which inhibit the production of a shed form of sCD as herein defined. In reducing the amount of shed molecule produced, the level of cell surface molecule should increase correspondingly. This should be advantageous to the cell. Advantageously, the inhibitor is a specific inhibitor of those one or more sCDs. Suitable inhibitors include alternative splicing inhibitors and/or enzymatic cleavage inhibitors. Advantageously, the inhibitor is an alternative splicing inhibitor. Such alternative splicing inhibitors are include for example inhibitors of exonic splicing enhancers (Fairbrother et al, Science, vol 297, 9<sup>th</sup> August 2002).

According to the above aspects of the invention, the production of any one or more sCDs present in the body fluid of an individual may be inhibited. Advantageously, the one or more sCDs are any one of those selected from the group consisting of the following: CD14, CD25, CD31, CD44, CD50, CD54, CD62E, CD62L, CD86, CD95, CD106, CD116, CD124, CD138, CD141, CD40L, CD8, CD23, CD30, CD40. More advantageously the sCD is CD1. Advantageously, the sCD is CD1 and the inhibitory agent is an alternative splicing inhibitor.

According to the above aspects of the invention, one or more inhibitory agents may be used for the prophylaxis or treatment of any one or more disease states selected from the group consisting of the following: infections, autoimmune disease, neoplastic, vascular endocrinological, metabolic, inflammatory degenerative, psychiatric psychological, traumatic, drug/toxin-related, bacterial, fungal, protozoan and viral infections, non-neoplastic disorders; pain; diabetes, obesity; anorexia; bulimia; asthma; pregnancy; endocrine; vascular; metabolic; gastro-intestinal; iatrogenic; psychiatric; psychocological; exercise-induced; diet-related; ME; degenerative; Parkinson's disease; thrombosis; atherosclerosis; acute heart failure; hypotension; hypertension; erectile dysfunction; urinary retention; metabolic bone diseases such as osteoporosis; angina pectoris; hepatitis; myocardial infarction; ulcers; allergies; rheumatoid arthritis; inflammatory bowel disease; irritable bowel syndrome benign prostatic hypertrophy; psychosis; psychiatric disorders; including anxiety; schizophrenia; manic depression;

delirium; dementia; severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome; and preferably tumours which can be benign or malignant cancers; breast cancer; myeloma; melanoma; bladder cancer; leukaemia; plasmocytoma and others, but most preferably appendicitis; Bence Jones  
5 Proteinuria; Chronic Myeloid Leukaemia; Colorectal cancer; chronic renal failure; Crohn's Disease; Diabetic Nephropathy; Cardiac pathology; Infection; Liver damage; Lymphoma; macrocytic anaemia; Prostate Cancer; Oligoclonal Banding and PE/DVT. Advantageously, the disease is tumourigenesis.

10 The invention will now be described by the following examples which are in no way limiting of the invention.

**Example 1. Figure 1.** Disease Groups. Multiples of ULN All sCD's included

15 Two values obtained (CD40L and CD30) for the individual, classified as normal, with a suspected drug overdose were omitted from the calculation of the upper limit of normal. The dilution factor for each sCD was fixed throughout the study. The results obtained are those of the diluted sample and have not been multiplied by the dilution  
20 factor. The absolute value of each data point was divided by the upper limit of normal (ULN) as defined above. Where the absolute value was greater than the dynamic range of the assay the result [9999] was recorded.

The limits indicated by each point are:

- Green  $\leq 1 \times \text{ULN}$
- 25 • Blue  $1 - 2 \times \text{ULN}$
- Red  $> 2 \times \text{ULN}$
- A white block indicates no data available.

**Example 2. Figure 2** Remove all sCD's that appear not to discriminate from the  
30 normals (sCD's 21; 102; 117; 126; 130; 26; 44v5; 44v6; 62P).

To simplify the diagram the above sCD plots were removed.

The data suggests (Figure 1.) that the concentration of some of these sCD may actually be lowered in disease. As we initially worked on the premise that there would be over-expression of these molecules in disease, samples have been diluted optimally to focus on high, rather than low concentrations.

5

**Example 3. Figure 3.** Disease Groups. Mode of Response for Remaining 20 sCD's

To simplify the data further the modal response for each disease group has been plotted. As the lymphoma and "oligoclonal-banding positive" group contain only a single subject, they have been omitted. Where there is no clear mode, both responses have been shown.

10

**Example 4. Figure 4.** Disease Groups. Mode of Response for remaining sCD's

15

Data has been ranked in order of increased expression.

**Example 5. Figure 5.** Disease Groups. Mode of Response for remaining sCD's

As for Figure 4. except responses have been classified as "normal" and "abnormal". Values >1 ULN have been classified as abnormal.

20

Both Figures 4 and 5 suggest that each disease state exhibit a unique pattern of elevated sCD expression.

**Example 6. Figure 6.** Disease Groups. Mode of Response for all sCD's

25

As for Figure 3 (except all sCD's are included).

The limits indicated by each point are:

- Green  $\leq 1 \times \text{MoM}$
- Blue  $1 - 2 \times \text{MoM}$
- Red  $> 2 \times \text{MoM}$

- A white block indicates no data available.

**Example 7.** Figure 7. Disease Groups. Mode of Response for all sCD's  
As for Figure 4.

**Example 8.** Figure 8. Disease Groups. Mode of Response for all sCD's

5

As for Figure 5. (except that values  $> 2$  MoM have been classified as abnormal).

Comparison of figures 5 and 8 illustrate the importance of determining the cut-off threshold values in order to obtain a defined pattern.

10

All publications mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described methods and system of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention. Although the present invention has  
15 been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in biochemistry, molecular biology and biotechnology or related fields are intended to be within the scope of the following  
20 claims.

## **Appendix.1**

# **Disease Associations of Soluble sCD2 to sCD157 Antigens Found in Human Serum.**

**Adrian Woolfson and César Milstein**

(note: this document was compiled from paper abstracts. Consequently when any numerical information such as mean serum level, SD, statistical significance or patient numbers is missing, this is because the relevant information was not specified in the paper abstract. All such information can, however, in principle be obtained by going back to the paper in question.

**sCD2 (LFA-2, T11)****HIV** (Schlesinger et al 1990)

Normal controls: (n=63)  
Asymptomatic HIV: (n=13)  
AIDS: (n=12)

Levels of serum sCD2 in asymptomatic HIV patients were very significantly reduced (mean absorbance at 492 nm: 0.00093 +/- 0.0048) as compared with normal controls (mean absorbance at 492 nm: 0.154 +/- 0.033). No further numerical data given. Serum sCD2 levels were elevated in 25% of patients. No numerical data given.

**Infectious Mononucleosis** (Motohashi 1993)

Levels of serum sCD2 were significantly increased in acute stages of the disease. No numerical data given.

**Kawasaki Disease** (Furukawa et al 1993)

No information given.

**sCD4 (L3T4, T4)****Infectious mononucleosis** (Yoneyama et al 1995)

Patients: (n=44)  
Normal controls: (n=not specified)

A very significant ( $p < 0.0001$ ) elevation in serum sCD4 levels was found in patients ( $19.3 \pm 0.9$ ) as compared with normal controls ( $8.1 \pm 0.2$ ).

**Wegener's granulomatosis** (D'Cruz et al 1999)

patients (n=23)  
healthy controls (n=20)

Median levels of serum sCD4 were significantly higher ( $p < 0.005$ ) in patients ( $17.0 \text{ U/ml}$ ) than in controls ( $15.2 \text{ U/ml}$ ). Levels correlated with disease activity scores. No further numerical data given.

**Nasopharyngeal carcinoma** (Kuo et al 1994)

Patients (n=12)  
Normal controls (n=12)  
Skin cancer controls (n=12)

Increased levels of sCD4 in patient group. No numerical data given.

**Acute pancreatitis** (Pezzilli et al 1994)

acute pancreatitis patients (n=35)  
healthy controls (n=not specified)

Levels of serum sCD4 were measured for 6 days following admission. Levels of sCD4 significantly decreased from day 2 to day 6 relative to normal controls. No numerical data given.

**Sjogren's syndrome** (Sawada et al 1992)

primary sjorgen's syndrome patients (n=28)  
secondary sjorgen's syndrome patients (n=13)  
normal controls (n=43)

Levels of serum sCD4 were significantly increased in patients with both primary and secondary disease as compared with controls. No numerical data given.

53

**Rheumatoid arthritis** (Kuryliszyn-Moskal et al 1998)

patients (n=80)  
healthy controls (n=30)

Serum levels of sCD4 were significantly higher in RA patients than in controls. No numerical data given.

**Polytransfused patients with beta-thalassemia major** (Lombardi et al 1994)

transfusion-dependent patients (n=45)  
normal controls (n=not specified)

Patients had lower values of serum sCD4 as compared with normal controls. No numerical data given.

**Pregnancy** (Watanabe et al 1996)

Pregnant mothers (1st, 2nd, 3rd trimesters and 1,4,7,10-12 months post-partum) (n=182)  
Healthy non-pregnant women (n=25)

The serum value of sCD4 decreased throughout pregnancy from the first trimester and recovered gradually after delivery. No numerical data given.

**Leishmaniasis** (Vitale et al 1994)

Levels of serum sCD4 were raised significantly in patients as compared with controls. Levels returned to the normal range after recovery. No numerical data given.

**IDDM** (Ng et al 1995)

IDDM patients (n=32)  
normal controls: (n=34)

Increased levels of serum sCD4 were found in only 1/32 of the patients. No numerical data given.

**Leishmaniasis** (Schriefer et al 1995)

Patients (n=not specified)

Pre-treatment levels of serum sCD4 were significantly ( $p < 0.05$ ) higher in patients than in healthy controls. No significant change following antimonial therapy. Levels of serum sCD4 fell significantly in patients that were refractory to drug treatment. No numerical data given.

**Scleroderma** (Sato et al 1996)

Patients with generalized morphea: (n=15)  
Controls (n=not specified)

Levels of serum sCD4 were significantly elevated in patients as compared with controls. No numerical data given.

**High dose chemotherapy and blood stem cell transplantation** (Ho et al 1994)

chemotherapy patients (n=12)

Highly statistically significant increase in serum sCD4 levels up to a maximum at day 21. No numerical data given.

**Polymyalgia rheumatica** (Salvarani et al 1994)

Patients with active polymyalgia rheumatica (n=19)  
Normal controls (n=not specified)

Decreased levels of serum sCD4 were found in patients as compared with controls. No numerical data given.

**Vogt-Koyanagi-Harada's disease** (Uchio et al 1999)

Active disease (n=24)  
Normal controls (n=20)

Significantly different levels in levels of serum sCD4 were found in the acute stages of the disease as compared with normal controls. No numerical data given.

**Kawasaki disease** (Furukawa et al 1991)

Patients (n=not specified)  
Controls (n=not specified)

Levels of serum sCD4 were significantly elevated in patients during acute stages of the disease as compared with controls. No numerical data given.

**Measles** (Furukawa et al 1991)

patients (n=not specified)  
controls (n=not specified)

Levels of serum sCD4 were significantly raised in patients during the acute stages of the disease. No numerical data given.

**Behcet's disease** (Uchio et al 1999) 55

Active Behcet's disease: (n=20)  
Inactive Behcet's disease: (n=15)  
Normal controls: (n=20)

Significantly increased levels of serum sCD4 were found in both the acute and convalescent stages of the disease as compared with normal controls. No numerical data given.

**sCD8 (T8)****Chronic lymphocytic leukemia (CLL)** (Beguin et al 1993)

CLL patients (n=42)  
Normal controls (n=31)

CLL patients had significantly ( $p < 0.001$ ) increased levels of serum sCD8 (510 +/- 191 U/ml) as compared with normal controls (234 +/- 89 U/ml).

**Graves disease** (Balazs et al 1994)

patients (n=58)  
normal controls (n=not stated)

Levels of serum sCD8 were significantly ( $p < 0.001$ ) elevated in Grave's disease patients (609 +/- 118 U/ml) as compared with normal controls (264.1 +/- 98.8). sCD8 levels returned to normal (278.7 +/- 89.1) following treatment with methimazole.

**Infectious mononucleosis** (Vinante et al 1994)

patients (n=55)  
normal controls (n=not specified)

Levels of serum sCD8 were very significantly elevated levels in patients (17,172 +/- 12,885 U/ml) as compared with normal controls (334 +/- 95 U/ml). By day 30, serum sCD8 levels fell to 20 +/- 21 U/ml.

**Multiple sclerosis** (Franciotta et al 1997)

Clinically active MS patients (n=16)  
Non-inflammatory neurological disease controls (n=not stated)  
Normal healthy controls (n=not stated)

Levels of serum sCD8 were significantly higher in MS patients than in healthy controls. Levels of sCD8 increased significantly ( $p = 0.002$ ) following therapy with 6-methylprednisolone and median serum sCD8 levels at day 21 were 1136 IU/ml (range 790-1416) versus 447 IU/ml (range 94-713) prior to therapy. No further numerical data given.

**Angioimmunoblastic lymphadenopathy (AILD)** (Pizzolo et al 1990)

patients (n=24)  
normal controls (n=not specified)

A significant ( $p < 0.01$ ) increase in serum sCD8 was detected in patients (978 +/- 646 U/ml) as compared with controls (334 +/- 95 U/ml).

**Advanced renal cell carcinoma** (Hobarth et al 1996)

patients (n=16)  
healthy controls (n=20)

Levels of serum sCD8 were significantly ( $p < 0.05$ ) elevated in patients (564 U/L) as compared with controls (336 U/L).

**Wegener's granulomatosis** (D'Cruz et al 1999)

patients (n=23)  
healthy controls (n=20)

Median levels of serum sCD8 were higher ( $p < 0.001$ ) in patients (260.5 U/ml) than in healthy controls (127 U/ml). Levels of serum sCD8 correlated with disease activity.

**Infectious mononucleosis** (Yoneyama et al 1995)

Patients: (n=44)  
Normal controls: (n=not specified)

Levels of serum sCD8 were very significantly ( $p < 0.0001$ ) elevated in patients (22366 +/- 270 U/ml) as compared with normal controls (219 +/- 10 U/ml).

**Acute graft-versus-host disease** (Bavaro et al 1994)

Patients with grade II-III aGvDH (n=not stated)  
Patients with grade 0-I aGvDH (n=not stated)

The serum sCD8 levels at day 21 in patients with grade II-III aGvDH were significantly ( $p < 0.002$ ) lower (447 IU/ml, range 94-713) than in patients with grade 0-I aGvDH (1136 IU/ml, range 790-1416).

**Juvenile rheumatoid arthritis** (Lipnick et al 1993)

afebrile JRA patients (n=49)  
normal controls (n=16)

Levels of serum sCD8 were significantly elevated in patients with severe JRA as compared with normal controls. No numerical data given.

**High dose chemotherapy and blood stem cell transplantation** (Ho et al 1994)

chemotherapy patients (n=12)

A highly statistically significant increase in serum sCD8 levels was observed up to a maximum at day 21. No numerical data given.

**Acute pancreatitis** (Pezzilli et al 1994)

acute pancreatitis patients	(n=35)
healthy controls	(n=not specified)

Levels of serum sCD8 were measured for 6 days following admission. Levels of serum sCD were significantly increased for the entire observation period relative to normal controls. No numerical data given.

**Kawasaki disease** (Furukawa et al 1991)

patients	(n=not specified)
controls	(n=not specified)

Levels of serum sCD8 were significantly raised in patients during acute stages of the disease. No numerical data given.

**Measles** (Furukawa et al 1991)

patients	(n=not specified)
controls	(n=not specified)

Levels of serum sCD8 were significantly elevated in patients during acute stages of the disease. No numerical data given.

**Sjogren's syndrome** (Sawada et al 1992)

primary sjorgen's syndrome patients	(n=28)
secondary sjorgen's syndrome patients	(n=13)
normals individuals	(n=43)

Levels of serum sCD8 were significantly decreased in patients with primary disease. No numerical data given.

**Lymphoproliferative diseases** (Frydecka 1994)

adult T cell leukemia	(n=not stated)
hairy cell leukemia	(n=not stated)
hodgkin's disease	(n=not stated)
non-hodgkin's lymphoma	(n=not stated)
chronic lymphocytic leukemia	(n=not stated)
controls	(n=not stated)

Increased levels of serum sCD8 were found in patients as compared with controls. No numerical data given.

**Polytransfused patients with beta-thalassemia major** (Lombardi et al 1994)

transfusion-dependent patients	(n=45)
normal controls	(n=not specified)

Patients had increased values of serum sCD8 as compared with normal controls. No numerical data given.

**Chronic viral hepatitis** (Onji et al 1994)

Patients with chronic active hepatitis, autoimmune hepatitis, primary biliary cirrhosis, acute hepatitis, fulminant hepatitis and liver cirrhosis	(n=not stated)
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Normal controls	(n=not stated)
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Levels of serum sCD8 were significantly higher in patients as compared with controls. No numerical data given.

**Tuberculosis** (Barlan et al 1995)

children with active pulmonary tuberculosis	(n=66)
healthy controls	(n=20)

Levels of serum sCD8 in children with active pTB were significantly ( $p < 0.05$ ) different to those in healthy controls. No numerical data given.

**Depression** (Maes et al 1996)

Major depression	(n=37)
Minor depression	(n=27)
Normal controls	(n=22)

Serum levels of sCD8 were significantly higher in depressed patients than in normal controls. 35% of depressed patients had increased ( $> 560$  U/ml) levels of sCD8. No further numerical data given.

**Solid tumours** (Orditurra et al 1998) 60

Patients (n=84)  
Normal controls (n=not stated)

Elevated levels of serum sCD8 were found in 32% of the patients. No numerical data given.

**Interferon therapy in chronic hepatitis C** (Maekawa et al 1997)

patients with chronic hepatitis C (n=not stated)

Levels of serum sCD8 correlated with levels of ALT during treatment and decreased with IFN treatment. No numerical data given.

**Asymptomatic HIV+** (Lenkei et al 1998)

HIV+ patients (n=not stated)  
Healthy controls (n=not stated)

Patients had elevated levels of serum sCD8 as compared with healthy controls. No numerical data given.

**Liver disease** (Hagihara et al 1997)

patients (n=not specified)  
normal controls (n=not specified)

Serum sCD8 levels were significantly ( $p<0.001$ ) higher in patients than in normal controls. Serum sCD8 levels were highest in acute hepatitis, followed by hepatocellular carcinoma, liver cirrhosis and chronic hepatitis. No further numerical data given.

**Gynecological malignancies** (Frydecka et al 1996)

Patients (n=30)  
Normal controls (n=not stated)

Levels of serum sCD8 were significantly increased before treatment as compared with normal controls. The decrease of tumor mass which followed radiotherapy correlated with serum levels of sCD8. No numerical data given.

**IDDM** (Ng et al 1995)

IDDM patients (n=32)  
normal controls (n=34)

Levels of serum sCD8 were elevated in 5/32 patients. No numerical data given.

**Nasopharyngeal carcinoma** (Kuo et al <sup>61</sup>1994)

Patients	(n=12)
Normal controls	(n=12)
Skin cancer controls	(n=12)

Levels of serum sCD8 were significantly elevated in patients as compared with controls. No numerical data given.

**IDDM** (Di Cesare et al 1994)

newly diagnosed IDDM patients	(n=33)
IDDM patients (duration of disease more than 1 year)	(n=29)
healthy siblings of IDDM patients	(n=37)
healthy controls	(n=19)

All 3 groups had significantly higher levels of serum sCD8 than normal controls ( $p < 0.0001$ ,  $P < 0.003$  and  $p < 0.03$  respectively). In 54% of newly diagnosed patients, sCD8 levels were significantly higher than in those with long-standing disease ( $p < 0.0005$ ) and healthy siblings ( $p < 0.002$ ). No further numerical data given.

**Localized Scleroderma** (Sato et al 1996)

Patients with generalized morphea:	(n=15)
Patients with systemic sclerosis	(n=not specified)

Levels of serum sCD8 were significantly elevated in patients with generalized morphea. Levels of sCD8 were significantly higher than those in patients with systemic sclerosis. No numerical data given.

**Leishmaniasis** (Schriefer et al 1995)

Patients	(n=not specified)
Controls	(n=not specified)

Pre-treatment levels of serum sCD8 were significantly ( $p < 0.05$ ) higher in patients than in healthy controls. Levels of serum sCD8 fell significantly ( $p < 0.05$ ) following antimonial therapy. No further numerical data given.

**Leishmaniasis** (Vitale et al 1994)

Patients	(n=not specified)
Controls	(n=not specified)

Serum sCD8 levels were raised significantly in patients as compared with controls. sCD8 levels returned to normal range after recovery. No numerical data given.

**Vogt-Koyanagi-Harada's disease** (Uchio et al 1999)<sup>62</sup>

patients with active disease (n=24)  
normal controls (n=20)

Levels of serum sCD8 were significantly different in both the acute and convalescent stages of the disease as compared with controls. No numerical data given.

**Polymyalgia rheumatica** (Salvarani et al 1994)

Active polymyalgia rheumatica: (n=19)  
Normal controls: (n=not specified)

Levels of serum sCD8 were significantly elevated in patients as compared with controls. In 15/15 patients sCD8 levels fell significantly following steroid therapy. No numerical data given.

**HIV-1 infection** (Jiang et al 1997)

Patients (n=not specified)  
Controls (n=not specified)

Serum sCD8 levels were elevated in HIV-1 patients as compared with controls. No numerical data given.

**Endometriosis** (Matalliotakis et al 1997)

Normal controls: (n=20)  
Endometriosis patients (pre-treatment with danazol) (n=10)  
Endometriosis patients (post-treatment with danazol for 6/12) (n=10)

Administration of the drug significantly reduced levels of serum sCD8 ( $p < 0.001$ ). No numerical data given.

**Behcet's disease** (Uchio et al 1999)

Active Behcet's disease: (n=20)  
Inactive Behcet's disease: (n=15)  
Normal controls: (n=20)

Significantly different levels of serum sCD8 were found in both the acute and convalescent stages of the disease as compared with normal controls. No numerical data or direction of change given.

**sCD14**

63.

**HIV** (Nockher et al 1994)

HIV-infected asymptomatic patients	(n=not specified)
HIV-infected with lymphadenopathy	(n=not specified)
ARC	(n=not specified)
AIDS	(n=not specified)
normal controls	(n=not specified)

Levels of serum sCD14 were significantly ( $p < 0.001$ ) elevated in HIV-infected asymptomatic patients and HIV-infected with lymphadenopathy ( $2.9 \pm 0.8$  mg/L) as compared with normal controls ( $2.2 \pm 0.8$  mg/L). A further significant rise in levels of serum sCD14 was seen in patients with ARC and AIDS ( $3.8 \pm 1.1$  and  $5.7 \pm 2.5$  mg/L respectively,  $p < 0.01$  in both cases).

**Systemic lupus erythematosus** (Nockher et al 1994)

patients with inactive phase (remission) SLE	(n=35)
SLE relapse	(n=17)
healthy controls	(n=65)

Increased levels of serum sCD14 were found in all SLE patients as compared with normal controls. Patients with SLE relapse had significantly ( $p < 0.0001$ ) higher levels ( $6.9$  mg/L) than those in remission ( $4.1$  mg/L). No further numerical data given.

**Acute Plasmodium falciparum malaria** (Wenisch et al 1996)

patients with complicated malaria	(n=45)
patients with gram negative septicaemia	(n=14)
healthy controls	(n=24)

Malaria patients with renal failure ( $n=16$ ) had significantly ( $p < 0.05$ ) higher levels of serum sCD14 ( $9453 \pm 1017$  micrograms/L) than those ( $n=29$ ) without renal failure ( $8116 \pm 1440$  micrograms/L). Both had higher levels of sCD14 than patients with septicaemia ( $6155 \pm 1635$  micrograms/L) and normal subjects ( $2776 \pm 747$  micrograms/L).

**Polytraumatized patients** (Kruger et al 1991)

polytraumatized patients	(n=16)
healthy controls	(n=30)

Levels of serum sCD14 were significantly decreased immediately following trauma ( $3.7 \pm 0.005$  micrograms/ml) as compared with healthy normal controls ( $1.7 \pm 0.3$  micrograms/ml). Levels of serum sCD14 in trauma patients increased to  $4.9 \pm 0.3$  micrograms/ml within 6 days. In patients with the most severe injuries these remained elevated for 14 days.

**Neonatal sepsis** (Blanco et al 1996)

neonates with positive blood culture (gram +ve)	(n=11)
neonates with positive blood culture (gram -ve)	(n=9)
normal newborns	(n=40)

Neonates with a positive blood culture had significantly ( $p < 0.001$ ) increased levels of serum sCD14 ( $3.20 \pm 1.26$  micrograms/L) as compared with normal controls. Neonates with gram +ve sepsis had significantly ( $p < 0.05$ ) lower levels of sCD14 ( $2.63 \pm 1.2$  micrograms/L) than those with gram -ve sepsis ( $4.04 \pm 1.0$  micrograms/L).

**Tuberculosis** (Juffermans et al 1998)

TB patients	(n=124)
contacts	(n=not specified)
declined during treatment	(n=not specified)
controls	(n=not specified)

Levels of serum sCD14 were elevated in patients with active TB as compared with controls, contacts and declined during treatment groups. No numerical data given.

**HIV** (Lien et al 1998)

HIV seropositive patients	(n=92)
seronegative controls	(n=not specified)

Levels of serum sCD14 were elevated in patients as compared with controls and highest in patients with advanced clinical and immunological disease. Patients with ongoing clinical events had significantly higher levels of serum sCD14 than symptomatic HIV-infected individuals without clinical events. sCD14 levels were especially elevated in individuals with mycobacterium avium complex. In a longitudinal study (n=26), increasing levels of serum sCD14 were associated with death. No numerical data given.

**Burns patients** (Kruger et al 1991) 65

patients	(n=5)
healthy controls	(n=not specified)

Patients had significantly elevated levels of serum sCD14 as compared with healthy controls. No numerical data given.

**Chronic inflammatory diseases** (Scherberich et al 1999)

patients	(n=not specified)
normal controls	(n=not specified)

Levels of serum sCD14 were elevated in patients (>3 microg/ml). No numerical data given.

**Periodontitis** (Hayashi et al 1999)

Patients	(n=38)
Healthy controls	(n=25)

Levels of serum sCD14 were significantly higher in patients than in healthy controls and decreased after treatment. No numerical data given.

**sCD15** (Lewis X-i antigen)**Non-small cell lung cancer** (Sato et al 1998)

untreated NSCLC patients (n=100)  
NO-1 patients (n=not specified)

Levels of serum sCD15 in patients with N2 were significantly ( $p=0.0049$ ) higher than those of NO-1 patients. No numerical data given.

**Liver disease** (Sunayama et al 1994)

Elevated levels of serum sCD15 were found in various liver disease patients. No numerical data given.

**Lung abscess** (Suzuki et al 1997)

patient (n=1)

Elevated serum sCD15 was found in the patient. Levels returned to the normal range post-operatively. No numerical data given.

**sCD16 (Fc gammaRIII)****Multiple myeloma** (Mathiot et al 1993)

myeloma patients	(n=165)
MGUS	(n=29)

Levels of serum sCD16 were significantly decreased in myeloma patients (25 a.u./ml) as compared with MGUS patients (144 a.u./ml). No further numerical data given.

**Multiple myeloma** (Mathiot et al 1993)

multiple myeloma patients (MM)	(n=165)
monoclonal gammopathies of unknown significance (MGUS)	(n=29)
normal controls	(n=20)

Levels of serum sCD16 were significantly ( $p=0.0001$ ) decreased in sera from patients with multiple myeloma as compared with normal controls and MGUS. In addition a stage-dependent decrease in serum sCD16 was observed, with a highly significant ( $p=0.004$ ) difference between stage I and II/III myeloma patients. No further numerical data given.

**Sepsis** (Kobold et al 1988)

patients	n=19
healthy controls	n=10

sCD16 correlated with disease severity ( $p<0.05$ ,  $r=0.53$ ). No numerical data given.

**Multiple myeloma and monoclonal gammopathy of unknown significance** (Mathiot et al 1996)

MGUS patients	(n=54)
multiple myeloma patients	(n=35)
healthy controls	(n=29)

Levels of serum sCD16 were significantly lower in multiple myeloma patients than in controls (83% had a value  $<1.3$  micrograms/ml as compared with only 17% of controls). A low sCD16 identified a group of MGUS which rapidly progress towards multiple myeloma (ie for a sCD16 level of 1.3, sensitivity and specificity were 70% and 79% respectively. No numerical data given.

sCD21 (CR2)

EBV mediated persistent polyclonal B-Cell lymphocytosis (Larcher et al 1995)

Patient (n=1)

Levels of serum sCD21 were elevated in the patient. No numerical data given.

**sCD23 (FceRII)****Chronic lymphocytic leukemia (CLL)** (Beguin et al 1993)

CLL patients	(n=42)
Normal controls	(n=31)

CLL patients had very significantly ( $p < 0.001$ ) increased levels of serum sCD23 (98.4 +/- 127.7) as compared with normal controls (0.9 +/- 0.3 U/ml). The values correlate with tumour mass and clinical stage.

**High risk IDDM subjects** (Avanzini et al 1988)

first degree relatives of IDDM patients	(n=not specified)
newly diagnosed patients	(n=not specified)
long-standing IDDM patients	(n=not specified)
normal controls	(n=not specified)

Serum sCD23 levels were significantly higher in all three experimental groups as compared with normal controls, median: 3.2 U/ml ( $p < 0.001$ ), 3.3 U/ml ( $p < 0.001$ ), 2.5 U/ml ( $p = 0.01$ ) respectively as compared with 1.2 U/ml in controls. Newly diagnosed patients had higher levels than those with long-standing disease ( $p = 0.026$ ).

**Hepatitis C (HCV) infection** (Bansal et al 1997)

HCV patients	(n=not specified)
alcoholic cirrhosis (AC)	(n=not specified)
healthy controls	(n=not specified)

Levels of sCD23 elevated in HCV (median 34.0 arbitrary units) as compared with alcoholic cirrhosis (median 10.1 units) and normal controls (11.1 units). HCV vs AC ( $p < 0.0004$ ). HCV vs controls ( $p < 0.0001$ ).

**Asthma** (Hoeger et al 1994)

asthma patients	(n=not specified)
healthy controls	(n=not specified)

Levels of serum sCD23 was lower ( $p < 0.05$ ) in patients with asthma (mean 4.93-2.29 micrograms/L) as compared with controls (6.92-4.11 micrograms/L). Levels of serum sCD25 normalized with clinical improvement. No further numerical data given.

**Graves' disease** (Sayinalp et al 1996)

Graves' disease patients	(n=15)
Non-toxic diffuse or multinodular goitre	(n=15)
toxic nodular goitre	(n=10)

46.7% Graves' disease patients had detectable levels of serum sCD23 (99.60 +/- 105.1). 47.89% of non-toxic diffuse or multinodular goitre patients had detectable levels of serum sCD23 (47.89 +/- 53.42) and 10% of patients with toxic nodular goitre (46.48 +/- 35.9). Levels of serum sCD23 were significantly ( $p < 0.02$ ) higher in Graves' patients than in other groups. No further numerical data given.

**Sjogren's syndrome** (Suzuki et al 1996)

patients	(n=13)
normal controls	(n=not specified)

Serum sCD23 levels were significantly ( $p < 0.01$ ) higher in patients (443.77 +/- 71.94 micrograms/L) than in normal controls (211.26 +/- 12.01). Values were higher in patients with complications.

**Helminth parasite infection** (Pritchard et al 1993)

patients	(n=not stated)
controls	(n=not stated)

Levels of serum sCD23 were significantly elevated levels in infected individuals. No numerical data given.

**Undifferentiated nasopharyngeal carcinoma** (Rousselet et al 1993)

UNPC patients treated with chemotherapy and radiotherapy (n=65)

Serum sCD23 levels showed a significant association with disease-free survival ( $p = 0.08$ ) and overall survival ( $p = 0.08$ ). No further numerical data given.

**Scleroderma** (Sato et al 1996)

Patients with generalized morphea:	(n=15)
Controls	(n=not specified)

Levels of serum sCD23 were significantly elevated in patients compared with controls. No numerical data given.

**Juvenile chronic arthritis** (Massa et al 1998)

patients with s-JCA	(n=22)
patients with ANA and p-JCA	(n=40)
healthy controls	(n=38)

Levels of serum sCD23 were increased in both patient groups as compared with healthy controls. No correlation with activity or severity was found. No numerical data given.

**Lepromatous leprosy** (Bansal et al 1998)

Patients with lepromatous leprosy	(n=not specified)
Patients with tuberculoid leprosy	(n=not specified)
Normal controls	(n=not specified)

Levels of serum sCD23 were significantly elevated in lepromatous leprosy patients as compared with tuberculoid leprosy patients and healthy controls. No numerical data given.

**Renal transplant patients with EBV virus reactivation** (Hornef et al 1997)

patients	(n=14)
control patients without reactivation	(n=10)

Levels of serum sCD23 were significantly ( $p<0.05$ ) elevated following reactivation.

**Coeliac disease** (Bansal et al 1997)

Coeliac patients	(n=not specified)
Control patients with non-specific upper GI symptoms	(n=not specified)

Levels of serum sCD23 were significantly ( $p<0.002$ ) decreased in coeliac disease patients. No further numerical data given.

**Haemorrhagic fever with renal syndrome** (Alexeyev et al 1997)

patients	(n=15)
controls	(n=not specified)

In the acute phase 11/15 patients had significantly increased levels of serum sCD23 ( $>91\text{U/ml}$ ), whereas in convalescence, in 8/10 of the patients the values normalized ( $r=0.597$ ,  $p=0.025$ ).

**Giant cell arteritis** (Roblot et al 1996)

GCA patients	(n=not specified)
controls	(n=not specified)

Levels of serum sCD23 levels were increased in patients and returned to normal within 24hrs following initiation of corticotherapy. No numerical data given.

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**Low grade non-Hodgkin's lymphoma** (Zinzani et al 1996)

newly diagnosed patients	(n=40)
healthy controls	(n=not specified)

Serum sCD23 was detected in 35/40 patients at diagnosis and levels were significantly ( $p=0.005$ ) increased as compared with normal controls. Patients with advanced stage disease presented with higher values of serum sCD23 than those with early stage disease ( $p=0.002$ ). All of the complete responders to chemotherapy (50%) showed a decrease in sCD23 levels. No further numerical values given.

**EBV infectious mononucleosis** (Hashimoto et al 1997)

patients	(n=not specified)
normal controls	(n=not specified)

Levels of serum sCD23 were elevated in patients as compared with normal controls. Levels decreased to normal during convalescence. No numerical data given.

**B-cell chronic lymphocytic leukemia (CLL)** (Knauf et al 1997)

newly diagnosed B-cell CLL patients	(n=105)
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High levels of serum sCD23 at diagnosis were linked with disease progression. No numerical data given.

**Primary sclerosing cholangitis (PSC)** (Bansal et al 1997)

PSC patients	(n=31)
Alcoholic cirrhosis (AC) patients	(n=12)
Normal controls	(n=20)

Levels of serum sCD23 were significantly elevated in PSC patients relative to AC patients ( $p<0.0001$ ) and normal controls ( $p<0.001$ ). No numerical data given.

**Nasal Allergy** (Ito et al 1998)

patients	(n=not specified)
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Serum levels of sCD23 were significantly reduced in patients treated with Azelastine for 4 weeks. No numerical data given.

**High risk IDDM subjects** (Kretowski <sup>73</sup> et al 1999)

first degree relatives of IDDM patients (n=28)  
age and sex matched healthy controls (n=28)

Median levels of serum sCD23 were lower in first degree relatives as compared with controls and statistically significant ( $p < 0.02$ ) in the subgroup of subjects with the lowest values of first phase insulin release. No numerical data given.

**B-cell Chronic lymphocytic leukemia CLL** (Molica et al 1999)

B-cell CLL patients (n=106)

Increased combined levels of serum sCD23 and serum beta-2 microglobulin were associated with high-risk disease. No numerical data given.

**Perennial allergic rhinitis** (Tanaka et al 1999)

patients (n=139)  
nonatopic controls (n=31)

Levels of serum sCD23 in patients were significantly ( $p < 0.0001$ ) higher than in controls. The level decreased significantly ( $p < 0.0001$ ) in patients who received immunotherapy. No further numerical data given.

**B-cell Chronic lymphocytic leukemia CLL** (Molica et al 1996)

B-cell CLL untreated patients (n=90)  
normal controls (n=15)

Levels of serum sCD23 were very significantly ( $p < 0.0005$ ) elevated in patients as compared with controls. This reflected tumour mass as defined either by clinical stage ( $p < 0.0005$ ) or bone marrow histology ( $p < 0.0005$ ). Life expectancy was significantly shorter in patients with high serum levels of sCD23 ( $p < 0.0005$ ). No further numerical data given.

**Atopic patient allergic to Parietaria** (Di Lorenzo et al 1999)

atopic patients (n=42)  
nonatopic controls (n=10)

Levels of serum sCD23 are elevated in atopic patients as compared with controls. No numerical data given.

**Post-renal transplantation** (Traindl et al 1994)

patients (n=not specified)

In the majority of patients, levels of serum sCD23 increased up to 3 days before the manifestation of an acute rejection (82% of cases) or infection episode (73% of cases). No further numerical data given.

**Rheumatoid arthritis** (Rezonzew et al 1994)

RA patients (n=not specified)

normal controls (n=not specified)

Patients had a significantly increased level of serum sCD23 as compared with controls. sCD23 levels in the serum correlated with RF titer ( $p < 0.0001$ ). No further numerical data given.

**Multilpe sclerosis** (Zaffaroni et al 1995)

MS patients (n=not specified)

Other neurological diseases (n=not specified)

Normal controls (n=not specified)

MS patients had a significantly elevated level of serum sCD23. No numerical data given.

**Localized scleroderma** (Sato et al 1996)

generalized morphoea (n=15)

linear scleroderma (n=22)

morphoea (n=12)

healthy controls (n=not specified)

Levels of serum sCD23 were highly elevated in patients with localized scleroderma as compared with healthy controls. Patients with generalized morphoea had the highest levels. No numerical data given.

**B-cell chronic lymphocytic leukemia** (Callea et al 1996)

advanced/progressive stage B-CLL (n=37)

smouldering B-CLL (n=10)

Normal controls (n=20)

Advanced/progressive stage B-CLL patients had significantly higher levels of serum sCD23 than normal controls. Levels of sCD23 directly correlated with tumour mass. Levels lowered significantly following chemotherapy. No numerical data given.

**Chronic lymphocytic leukemia (CLL)** (Santari et al 1996)

CLL patients (n=153)  
controls (n=not specified)

Levels of serum sCD23 were a prognostic factor for survival ( $p=0.03$ ). Patients with a sCD23 value above median value ( $>574\text{U/ml}$ ) had a significantly ( $p=0.0001$ ) worse prognosis than those with lower values (median survival 53 vs 100+ months). Serum sCD23 doubling time increased the risk of death by a factor of 3.2 ( $p=0.001$ ). Amongst stage A patients ( $n=100$ ), sCD23 levels at the time of study entry were the sole variable predictive of disease progression. Patients with values  $> 574\text{ U/ml}$  had a median progression time of 42 months vs 88 months for those with lower levels ( $p=0.0001$ ). Stage A patients who doubled their sCD23 level exhibited a 15-fold increased risk of progression ( $p=0.0001$ ). No further numerical data given.

**Polytransfused patients with beta-thalassemia major** (Lombardi et al 1994)

transfusion-dependent patients (n=45)  
normal controls (n=not specified)

Patients had increased values compared to normal controls. Serum levels of sCD23 correlated directly with annual transfusion requirement. No numerical data given.

**sCD25 (sIL-2R alpha)****Infectious mononucleosis** (Vinante et al 1994)

patients (n=55)  
controls (n=not specified)

Levels of serum sCD25 were very significantly elevated levels in patients (2,922 +/- 2,813 U/ml) vs controls (331 +/- 115 U/ml). No further numerical data given.

**Angioimmunoblastic lymphadenopathy (AILD)** (Pizzolo et al 1990)

patients (n=24)  
normal controls (n=not specified)

Very high levels ( $p < 0.001$ ) of serum sCD25 were found in 100% of patients (6315 +/- 3374 U/ml) as compared with 271 +/- 112 U/ml in normal controls.

**Ulcerative colitis** (Dalekos et al 1998)

patients with active disease (n=32)  
patients with inactive disease (n=43)

Mean serum levels of sCD25 were significantly ( $p = 0.0001$ ) higher in active disease (604.3 +/- 213) than in inactive disease (411.5 +/- 165.1).

**Acute asthma** (Kim et al 1998)

patients with acute attack (n=50)

Mean serum levels of sCD25 were significantly ( $p < 0.01$ ) higher at acute exacerbation (854 +/- 248 U/ml) than at clinical remission (676 +/- 211 U/ml). Levels correlated positively with the severity of exacerbation ( $r = 0.47$ ,  $p < 0.01$ ).

**Chronic lymphocytic leukemia (CLL)** (Beguin et al 1993)

CLL patients (n=42)  
Normal controls (n=31)

CLL patients had significantly ( $p < 0.001$ ) increased levels of sCD25 (6080 +/- 7030 as compared with 1420 +/- 640 pg/ml in normal controls).

**Chronic hepatitis B infection** (Sawayama et al 1999)

patients	(n=105)
healthy controls	(n=21)

Serum sCD25 levels were significantly ( $p<0.05$ ) higher in chronic HBV-infected patients with chronic hepatitis (508 +/- 310 U/ml) and liver cirrhosis (543 +/- 283 U/ml) than in healthy controls (331 +/- 106 U/ml). Moreover, sCD25 levels were significantly ( $p<0.01$ ) higher in patients with chronic hepatitis or liver cirrhosis than in asymptomatic HBV carriers (341 +/- 150 U/ml).

**Wegener's granulomatosis** (D'Cruz et al 1999)

patients	(n=23)
healthy controls	(n=20)

Median levels of serum sCD25 were significantly higher ( $p<0.01$ ) in patients (789.5 U/ml) than in healthy controls (551 U/ml). Levels correlated with disease activity scores.

**Chronic hepatitis B infection** (Sawayama et al 1999)

patients	(n=105)
healthy controls	(n=21)

Serum sCD25 levels were significantly ( $p<0.05$ ) higher in chronic HBV-infected patients with chronic hepatitis (508 +/- 310 U/ml) and liver cirrhosis (543 +/- 283 U/ml) than in healthy controls (331 +/- 106 U/ml). Serum sCD25 levels were also significantly ( $p<0.01$ ) higher in patients with chronic hepatitis or liver cirrhosis than in asymptomatic HBV carriers (341 +/- 150 U/ml). Serum sCD25 levels in most patients decreased to the same level as asymptomatic HBV carriers and healthy controls at 48 weeks after the end of treatment.

**Myeloproliferative disorders** (Bourantas et al 1999)

patients	(n=55)
controls	(n=not stated)

High levels of serum sCD25 were found in all patients. The elevation was found to be progressive. No numerical data given.

**Pancreatic adenocarcinoma** (Gansauge et al 1998)

Patients	(n=not specified)
Normal controls	(n=not specified)

Serum sCD25 levels were significantly higher in cancer patients than in normal control subjects or in chronic pancreatitis patients. Patients with adenocarcinoma of the pancreas with low sCD25 levels (<500U/ml) lived significantly ( $p<0.01$ ) shorter than patients with levels above 500U/ml. No further numerical data given.

**Colorectal cancer** (Saito et al 1998)

patients (n=38)  
healthy controls (n=98)

Serum levels of sCD25 were significantly ( $p < 0.05$ ) higher in patients than in controls. Levels were markedly elevated in patients with stage IV cancer, with Duke's Stage D cancer, or with liver metastasis. No further numerical data given.

**Renal diseases** (Sugimoto et al 1998)

patients (n=not specified)  
healthy controls (n=not specified)

Serum sCD25 levels were significantly higher in patients with renal diseases than in healthy controls. No numerical data given.

**Ovarian cancer** (Gebauer et al 1998)

Changes in levels of serum sCD25 post-surgery may be a useful prognostic factor. No other information given.

**IDDM** (Ng et al 1995)

normal controls: (n=34)  
IDDM: (n=32)

Levels of serum sCD25 were elevated in 3/32 patients. No numerical data given.

**Systemic lupus erythematosus** (Swaak et al 1995)

patients (n=69)

Levels of serum sCD25 were elevated during all periods of increased disease activity. No numerical data given.

**IL-2 therapy** (Bogner et al 1992)

pediatric and adult cancer patients receiving IL-2 therapy (n=51)

A statistically significant dose effect of IL-2 on serum levels of sCD25 was observed. No numerical data given.

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**Non-Hodgkin's lymphoma** (Perez-Encinas et al 1998)

patients (n=not specified)

sCD25 is a sensitive serum marker of tumour burden. No numerical data given.

**B-cell chronic lymphocytic leukemia** (Callea et al 1996)

advanced/progressive stage B-CLL	(n=37)
smouldering B-CLL	(n=10)
Normal controls	(n=20)

Advanced/progressive stage B-CLL patients had significantly higher levels of serum sCD25 than smouldering B-CLL and normal controls. Levels directly correlated with tumour mass. Levels of sCD25 were lowered significantly following chemotherapy. No numerical data given.

**Juvenile rheumatoid arthritis** (Lipnick et al 1993)

afebrile JRA patients	(n=49)
normal children	(n=16)

Statistically increased levels of serum sCD25 were found in patients with severe JRA. No numerical data given.

**Lymphoproliferative diseases** (Sawada et al 1992)

adult T cell leukemia	(n=not stated)
hairy cell leukemia	(n=not stated)
hodgkin's disease	(n=not stated)
non-hodgkin's lymphoma	(n=not stated)
chronic lymphocytic leukemia	(n=not stated)

Increased levels of serum sCD25 were found in all groups of patients. No numerical data given.

**High dose chemotherapy and blood stem cell transplantation** (Ho et al 1994)

chemotherapy patients (n=12)

A highly statistically significant increase in levels of serum sCD25 were found from day 7 to 21. No numerical data given.

**Cervical neoplasia** (Hildensheim et al 1997)

Levels of serum sCD25 were positively associated with cervical neoplasia. No further information given.

**Hematologic malignancies** (Srivastava et al 1994)

hairy cell leukemia	(n=not stated)
acute myelomonocytic leukemia	(n=not stated)
acute myelocytic leukemia	(n=not stated)
B chronic lymphocytic leukemia	(n=not stated)
prolymphocytic leukemia	(n=not stated)
non-T/non-B acute lymphoblastic leukemia	(n=not stated)
B-acute lymphoblastic leukemia	(n=not stated)
mixed lineage acute lymphoblastic leukemia	(n=not stated)
T chronic lymphocytic leukemia	(n=not stated)
active mycosis fungoides	(n=not stated)

Elevated levels of serum sCD25 were found in all of the patient groups. Reduced levels were found in hairy cell leukemia, pre-T acute lymphoblastic leukemia and active mycosis fungoides patients in remission. No numerical data given.

**Polytransfused patients with beta-thalassemia major** (Lombardi et al 1994)

transfusion-dependent patients	(n=45)
normal controls	(n=not specified)

Patients had increased values of serum sCD25 as compared with normal controls. Serum levels of sCD25 correlated directly with annual transfusion requirement. No numerical data given.

**Disease exacerbations in systemic lupus erythematosus** (Spronk et al 1994)

Patients (n=6)

During major disease exacerbations, levels of serum sCD25 increased significantly ( $p < 0.001$ ). No further numerical data given.

**Major depression** (Sluzewska et al 1996)

patients	(n=49)
normal controls	(n=15)

Serum sCD25 levels were significantly elevated in patients as compared with controls. No further numerical data given.

**Solid tumours** (Oditurra et al 1998)

Patients	(n=84)
Normal controls	(n=not stated)

High levels of serum sCD25 were found in 82% of the patients. No numerical data given.

**Malignant lymphoma** (Motokura et al 1995)

patients (33 non-Hodgkin's, 3 Hodgkins)	(n=36)
controls	(n=not stated)

The serum level of sCD25 was significantly elevated in patients with active disease as compared to those in remission and correlated with the clinical stage of the lymphoma. No numerical data given.

**Tuberculosis** (Barlan et al 1995)

children with active pulmonary tuberculosis	(n=66)
healthy controls	(n=20)

There were significant ( $p < 0.05$ ) differences between the levels of serum sCD25 in children with active pTB and healthy controls. No numerical data given.

**Gynecological malignancies** (Frydecka et al 1996)

Patients	(n=30)
Normal controls	(n=not stated)

Levels of serum sCD25 were significantly increased before treatment as compared with normal controls. No numerical data given. The decrease of tumor mass following radiotherapy, correlated with serum levels of sIL-2R. No numerical data given.

**Polymyalgia rheumatica** (Salvarani et al 1994)

Active Polymyalgia rheumatica:	(n=19)
Normal controls:	(n=not specified)

Levels of sCD25 were significantly elevated levels in patients as compared with controls. In 15/15 patients levels fell significantly 7 days following steroid therapy. No numerical data given.

**Psoriasis** (De Rie et al 1996)

Patients treated with cyclosporin A:	(n=17)
Patients treated with FK506	(n=5)

Levels of serum sCD25 correlated with disease activity ( $r_s = 0.89$ ;  $s_p < 0.05$ ). No numerical data given.

**Behcet's disease** (Uchio et al 1999)

Active Behcet's disease: (n=20)  
Inactive Behcet's disease (n=15)  
Normal controls: (n=20)

Significantly increased levels of serum sCD25 were found in both the acute and convalescent stages of the disease as compared with normal controls. No numerical data given.

**Acute pancreatitis** (Pezzilli et al 1994)

acute pancreatitis patients (n=35)  
healthy controls (n=not specified)

Levels of serum sCD25 were measured for 6 days following admission. Levels significantly increased for the entire observation period relative to normal controls. Serum sCD25 concentrations were significantly higher in patients with severe pancreatitis than in those with the mild form of the disease. No numerical data given.

**Nasopharyngeal carcinoma** (Kuo et al 1994)

Patients (n=12)  
Normal controls (n=12)  
Skin cancer controls (n=12)

Increased levels of serum sCD25 were found in the patient group (early stages of the disease). No numerical data given.

**Leishmaniasis** (Schriefer et al 1995)

patients (n=not specified)  
healthy controls (n=not specified)

Pre-treatment levels of serum sCD25 were significantly ( $p<0.05$ ) higher in patients than in healthy controls. Levels fell significantly ( $p<0.05$ ) following antimonial therapy. The pre-treatment levels of sCD25 in responders and patients refractory to antimonial therapy differed significantly ( $p=0.02$ ), suggesting that they could be used as predictors of antimonial therapy response. No further numerical data given.

**Vogt-Koyanagi-Harada's disease** (Uchio et al 1999)

Active disease: (n=24)  
Normal controls: (n=20)

Levels of serum sCD25 were significantly elevated in the acute stages of the disease as compared with controls. No numerical data given.

**Pulmonary mycobacterial diseases** (Tada et al 1999)

untreated pTB patients	(n=24)
treated multi-drug resistant intractable pTB	(n=7)
pulmonary non-tuberculous mycobacteriosis	(n=27)
controls	(n=not specified)

Serum sCD25 levels were elevated in patients with pulmonary mycobacterial diseases and in untreated pTB patients as compared with controls. No numerical data given.

**Gastric carcinoma** (Maeta et al 1998)

Patients	(n=91)
normal controls	(n=not specified)

Pre-operative levels of serum sCD25 were significantly higher than in normal controls and levels were a useful indicator of lymph node involvement. Patients with progressive post-operative increases in levels had both a significantly higher frequency of post-operative relapse and a poor prognosis. No numerical data given.

**Gastric cancer** (Saito et al 1999)

patients	(n=121)
normal controls	(n=not specified)

Pre-operative levels of serum sCD25 in patients with gastric cancer were significantly higher than those in normal controls. An elevated level of sCD25 was significantly correlated with clinicopathological features, including lymph node metastasis. The post-operative survival time of patients with elevated levels of sCD25 was significantly lower than those with normal levels.

**Neuroleptic treatment in schizophrenia** (Muller et al 1997)

schizophrenic patients	(n=39)
healthy controls	(n=42)

During neuroleptic treatment there was a significant increase in serum sCD25 levels. No further numerical data given.

**Brain damage** (Rogers et al 1998)

Patients	(n=not stated)
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Serum levels of sCD25 were significantly elevated in individuals with unilateral brain damage. No numerical data given.

**Bone marrow transplant** (Liem et al 1998)

Patients (n=46)

Serum levels of sCD25 were significantly increased following transplantation. Increased level were correlated with graft vs host disease. No numerical data given.

**Heatstroke** (Hammammi et al 1998)

patients (n=not specified)

controls (n=not specified)

Serum levels of sCD25 were elevated in patients as compared with controls. No numerical data given.

**Autoimmune rheumatic disease** (Sfikakis et al 1999)

Rheumatoid arthritis (RA), systemic sclerosis (SSc) and SLE patients (n=75)

Levels of serum sCD25 levels in patients with active RA, SSc and SLE were almost double the normal level. No numerical data given.

**Cervical neoplasia** (Ung et al 1999)

Low grade squamous intraepithelial lesions (LSIL) (n=191)

High grade squamous intraepithelial lesions (HSIL) (n=130)

Cervical cancer (n=37)

normal controls (HPV negative) (n=120)

Women with LSIL had higher serum sCD25 levels than controls (OR for upper quartile of sCD25, 2.3; 95% CI, 1.1-5.2; comparing LSIL cases with controls. Women diagnosed with HSIL were similar to the LSIL group (OR for upper quartile of sCD25, 1.1; 95% CI, 0.5-2.4; comparing HSIL cases with LSIL cases. Those with cancer had higher levels than subjects with an HSIL diagnosis (OR for upper quartile of sCD25 = 1.8; 95% CI, 0.5-7.1).

**B cell chronic lymphocytic leukemia** (Mavridis et al 1998)

B-CLL patients (n=20)

Serum sCD25 levels were significantly elevated in patients. There was an excellent correlation between levels and disease activity. Patients with aggressive disease had increased levels. Patients who responded to therapy and with improved clinical status had decreased sCD25 levels. No numerical data given.

**Hepatocellular cancer** (Izzo et al)

patients with HCC	(n=99)
healthy volunteers	(n=174)

Serum sCD25 levels were elevated in 98/99 patients ( $p < 0.01$ ). Serum sCD25 levels returned to normal in 27/99 patients after treatment. No numerical data given.

**Behcet's disease** (Alpsoy et al 1998)

patients	(n=32)
healthy controls	(n=20)

Serum sCD25 levels in patients with active disease were significantly higher than in either patients with inactive disease ( $p < 0.001$ ) or the control group ( $p < 0.05$ ).

**Multiple sclerosis** (Bilinska et al 1999)

Patients	(n=not stated)
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Levels of serum sCD25 were significantly increased in patients as compared with normal controls. No numerical data given.

**sCD27****B-cell chronic lymphoblastic leukemia (CLL)** (Molica et al 1998)

B-cell CLL (previously untreated patients) (n=82)  
Healthy controls (n=not specified)

Serum sCD27 levels were significantly ( $p<0.0001$ ) higher in CLL patients (2150 U/ml) than in controls (220 U/ml). Changes in sCD27 correlated with clinical stage.

**B-cell malignancies** (van Oers et al 1993)

Patients (n=not specified)

Very high levels of serum sCD27 were found in patients with B cell malignancies (6,000U/ml) as compared with normal levels ( $<190\text{U/ml}$ ). There was a strong correlation with tumour load. The highest levels were found in CLL and low grade non-Hodgkin's lymphomas.

**Systemic lupus erythematosus** (Font et al 1996)

SLE patients (n=70)  
Healthy controls (n=20)

The mean level of sCD27 was significantly ( $p=0.02$ ) higher in SLE patients ( $48.29 \pm 23.86\text{U}$ ) as compared with controls ( $36.13 \pm 7.48$ ). Patients with active SLE ( $58.20 \pm 31.06\text{U}$ ) had significantly ( $p<0.01$ ) higher levels than those in remission ( $42.77 \pm 16.71\text{U}$ ).

**Psoriasis** (De Rie et al 1996)

Patients treated with cyclosporin A: (n=17)  
Patients treated with FK506 (n=5)

Levels of serum sCD27 were elevated in patients and decreased following treatment. No numerical data given.

**Graves' disease** (Kallio et al 1998)

Patients (n=not stated)

Levels of serum sCD27 were elevated in untreated Graves' disease. Levels normalized with treatment. No numerical data given.

**Systemic lupus erythematosus** (Swaak et al 1995)

Patients (n=69)

Levels of serum sCD27 were elevated in all periods of increased disease activity. No numerical data given.

**Lymphatic filariasis** (Yazdanbakhsh et al 1993)

patients (n=145)

Levels of serum sCD27 were significantly ( $p < 0.002$ ) elevated in elephantitis and microfilaremic patients as compared with endemic normals. No further numerical data given.

**sCD30 (Ki-1)****HIV** (Pizzolo et al 1997)

acute primary HIV infection	(n=17)
following seroconversion	(n=13)
normal controls	(n=not specified)

Levels of serum sCD30 during acute infection were consistently very significantly ( $p<0.0001$ ) elevated ( $137.58 \pm 120.33$ ) as compared with normal controls ( $6.4 \pm 5.4$  U/ml). Levels of serum sCD30 decreased significantly ( $p=0.0018$ ) following sero-conversion ( $49.1 \pm 66.17$ ) as compared with acute infection levels.

**Hashimoto's thyroiditis** (Okumura et al 1997)

HS patients	(n=37)
normal subjects	(n=21)

Levels of serum sCD30 were significantly ( $p<0.0001$ ) elevated in HS patients ( $29.9 \pm 26.0$  U/ml) as compared with controls ( $7.1 \pm 4.5$  U/ml). Levels were significantly higher ( $p<0.05$ ) in patients with transient destructive thyrotoxicosis caused by aggravation of the disease ( $48.8 \pm 34.4$  U/ml) than in euthyroid patients ( $24.2 \pm 19.4$  U/ml).

**Rheumatoid arthritis** (Wang et al 1997)

RA patients	(n= 25)
Normal controls	(n=21)

Levels of serum sCD30 were significantly ( $p<0.05$ ) elevated in RA patients ( $15.2 \pm 2.1$  U/ml) as compared with normal controls ( $8.8 \pm 0.9$  U/ml).

**Wegner's granulomatosis (WG)** (Wang et al 1997)

WG patients	(n=57)
Normal controls	(n=21)

Levels of serum sCD30 were very significantly ( $p<0.0001$ ) elevated in generalized ( $22.5 \pm 1.5$  U/ml) but not initial phase ( $12.1 \pm 4.0$  U/ml) WG patients, as compared with normal controls ( $8.8 \pm 0.9$  U/ml). Levels declined significantly ( $p=0.0001$ ) in patients (n=11) that were in remission ( $29.1 \pm 1.9$  U/ml to  $15.9 \pm 1.8$  U/ml).

**Multiple sclerosis** (McMillan et al 1998)

Primary progressive MS	(n=not specified)
Secondary progressive MS	(n=not specified)
Relapsing/remitting MS (RRMS)	(n=not specified)
Inflammatory neurological disease patients (IND)	(n=not specified)
Non-inflammatory neurological disease (NIND)	(n=not specified)

Higher levels of serum sCD30 were detected in all MS subgroups and IND patients as compared with NIND controls. RRMS patients had significantly ( $p=0.04$ ) higher levels (45.7 U/ml) than those in relapse (18.3 U/ml).

**Atopic disorders** (Latzka et al 1999)

Atopic patients	(n=60)
Normal controls	(n=59)

The mean level of serum sCD30 was 75 U/ml (SD 110 U/ml) in patients as compared with 34 U/ml (SD 59 U/ml) in controls. Serum levels of sCD30 were elevated in 65% of patients as compared with 32% of the controls.

**Angioimmunoblastic lymphadenopathy (AILD)** (Pizzolo et al 1990)

patients	(n=24)
normal controls	(n=not specified)

Very high levels of serum sCD30 were detected 19/24 patients (722 +/- 895 U/ml) as compared with the lack of detectable levels in controls.

**Childhood tuberculosis** (hanekom et al 1999)

patients	(n=91)
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High levels of serum sCD30 were found at diagnosis (median 98 U/L, range 11 to 1,569 U/L). Levels were statistically higher in patients with nutritional compromise. Levels of sCD30 decreased following vitamin A therapy.

**Hodgkin's disease** (Nadali et al 1994)

patients	(n=117)
controls	(n=not specified)

Serum sCD30 levels were significantly increased ( $p<0.0001$ ) in 87.2% of patients (mean +/- SD 108 +/- 134 U/ml) as compared with controls (5.3 +/- 5.7 U/ml). Levels correlated with the stage of disease.

**Atopic dermatitis (AD)** (Bengtsson et al 1997)

AD patients	(n=49)
healthy non-atopic controls	(n=94)

Levels of serum sCD30 in AD were significantly ( $p < 0.001$ ) higher in patients (29 U/ml, range 1-708 U/ml) as compared with controls (11 U/ml, range 1-1042).

**Chronic hepatitis B infection** (Fattovich et al 1996)

patients	(n=90)
healthy carriers	(n=not specified)
normal controls	(n=not specified)

Significantly ( $p < 0.00005$ ) elevated levels (median value 26.7 U/ml) of serum sCD30 were detected in 57/90 (63%) of patients as compared with healthy carriers (median 10.5 U/ml) and normal controls (3 U/ml,  $p < 0.00001$ ). Raised levels correlated with acute illness.

**Anaplastic large-cell lymphoma** (Nadali et al 1995)

patients	(n=24)
controls	(n=not specified)

Significantly ( $p < 0.0001$ ) elevated levels of serum sCD30 (median 842.5 U/ml, range 16-37,250) at diagnosis were found in 23/24 patients as compared with controls. The highest median value was observed in patients with T-cell-type ALCL (1,690 U/ml). No further numerical data given.

**Systemic lupus erythematosus** (Caligaris-Cappio et al 1995)

SLE patients	(n=21)
Undifferentiated connective tissue disease (UCTD)	(n=17)
normal donors	(n=40)

Serum sCD30 values were (53.84  $\pm$  58.24 U/ml) in SLE, (22.65  $\pm$  9.82 U/ml) in UCTD, and (5.3  $\pm$  5.7 U/ml) in normal controls. Levels of serum sCD30 in SLE patients were significantly ( $p < 0.0005$ ) elevated as compared with controls and UCTD ( $p < 0.05$ ). Levels of serum sCD30 were directly related to disease activity ( $p < 0.002$ ).

**Infectious mononucleosis** (Vinante et al 1994)

patients	(n=55)
controls	(n=not specified)

Levels of sCD30 were highly elevated levels in patients (477  $\pm$  452 U/ml) as compared with controls (4.9  $\pm$  6.4 U/ml). By day 30, levels in patients fell to 20  $\pm$  21 U/ml. No further numerical data given.

**Graves' disease** (Okumura et al 1997)

patients	(n=71)
normal subjects	(n=21)

Levels of sCD30 were significantly ( $p < 0.0001$ ) elevated in Graves' disease patients ( $29.2 \pm 25.2$  U/ml) as compared with controls ( $7.1 \pm 4.5$  U/ml). Levels were significantly ( $p < 0.001$ ) higher in thyrotoxic patients ( $41.7 \pm 31.2$  U/ml) than in remission ( $15.8 \pm 11.0$  U/ml).

**Atopic dermatitis** (Bottari et al 1999)

sCD30 elevated in patients. Levels decreased following cyclosporin A treatment. No numerical data given.

**HIV infected hemophiliacs** (Sabin et al 1997)

hemphiliac men	(n=85)
controls	(n=not specified)

Serum sCD30 levels were elevated in patients. No numerical data given.

**Anaplastic large-cell lymphoma (ALCL)** (Zinzani et al 1998)

previously untreated ALCL-CT patients	(n=38)
previously untreated ALCL-HL patients	(n=32)
stage matched patients with Hodgkin's disease (HD)	(n=50)
healthy controls	(n=not specified)

Levels of serum sCD30 were highly elevated in HD patients as compared with healthy controls. Median sCD30 levels in patients with ALCL-CT and ALCL-HL were 18 and 7 times higher respectively than in patients with HD. The serum sCD30 level normalised with treatment. No numerical data given.

**Hodgkin's disease** (Nadali et al 1998)

patients	(n=303)
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Serum sCD30 levels were correlated with stage, presence of B symptoms and tumour burden. High serum sCD30 levels entailed a higher risk of poor outcome. No numerical data given.

**Kawasaki disease** (Vagliasindi et al 1997)

Patients	(n=10)
Controls	(n=not specified)

Very high levels of serum sCD30 were found in patients. No numerical data given.

**sCD31 (PECAM-1)****Thrombolytic therapy in acute myocardial infarction (AMI)** (Serebruany et al 1999)

AMI patients	(n=23)
healthy controls	(n=22)

Levels of sCD31 increased significantly ( $p=0.02$ ) 3 hrs following thrombolysis, followed by a significant ( $p=0.03$ ) decrease 24hrs later. No further numerical data given.

**sCD32 (FcγRII)****Multiple myeloma** (Tartour et al 1995)

patients (n=not specified)

Levels of serum sCD32 levels slightly increased in MM patients. No numerical data given.

**Heparin-induced thrombocytopenia** (Saffroy et al 1997)

No data given.

**sCD35 (CR1)****End-stage renal failure on dialysis** (Pascual et al 1993)

patients	(n=36)
normal controls	(n=31)

Levels of serum sCD35 were significantly ( $p < 0.0001$ ) elevated in patients ( $54.8 \pm 11.7$  ng/ml) as compared with normal controls ( $31.4 \pm 7.8$  ng/ml).

**Liver cirrhosis** (Pascual et al 1993)

patients	(n=22)
normal controls	(n=31)

Levels of serum sCD35 were significantly ( $p < 0.0001$ ) elevated in patients ( $158.3 \pm 49.9$  ng/ml) as compared with normal controls ( $31.4 \pm 7.8$ ). The mean sCD35 dropped significantly ( $p < 0.001$ ) from ( $181 \pm 62.7$  ng/ml) to ( $52.1 \pm 24.0$  ng/ml) in 9 patients undergoing liver transplantation.

**Leukemia** (Sadallah et al 1999)

patients	(n=180)
normal controls	(n=not specified)

50% of patients had levels of serum sCD35 above the normal range. Highest levels were in T-ALL patients (n=17). No numerical data given.

**sCD38****Multiple myeloma** (Funaro et al 1996)

Serum sCD38 levels are detectable in these patients. No numerical data given.

**AIDS** (Funaro et al 1996)

Levels of serum sCD38 are detectable in these patients. No numerical data given.

**sCD40****Chronic renal failure, haemodialysis, CAPD** (Schwabe et al 1999)

haemodialysis (HD) patients	(n=22)
CAPD (chronic ambulatory peritoneal dialysis patients	(n=10)
healthy controls	(n=41)

Levels of serum sCD40 were highly elevated in all patients with impaired renal function. HD patients had up to a 100-fold elevated ( $8.32 \pm 4.11$  ng/ml) level of serum sCD40 levels as compared with healthy controls ( $0.14 \pm 0.12$  ng/ml). CAPD patients had increased levels of  $3.58 \pm 2.4$  ng/ml. No further numerical data given.

**sCD44****Non-Hodgkin's lymphoma** (Snachez et al 1999)

patients with stage IV non-Hodgkin's lymphoma	(n=48)
controls	(n=80)

Mean serum levels of sCD44 were 398 +/- 160 ng/ml in patients as compared with 223 +/- 5 ng/ml in controls. No further numerical data given.

**Acute leukemia and myelodysplastic syndromes** (Nasu et al 1998)

AML	(n=18)
ALL	(n=16)
CML	(n=18)
MDS	(n=43)
normal controls	(n=51)

Serum sCD44 levels as compared with normal controls (24.6 ng/ml) were significantly elevated in: AML (99.0 ng/ml,  $p=0.0001$ ), ALL (427.8 ng/ml,  $p=0.0001$ ), MDS (54.9 ng/ml,  $p=0.0071$ ) and CML (97.5 ng/ml,  $p=0.0001$ ). In patients with acute leukemia, serum sCD44 decreased significantly in response to treatment and reached nearly normal levels after complete remission ( $p=0.0005$  in AML and  $p=0.0032$  in ALL).

**Colorectal cancer** (Weg-Remers et al 1998)

colorectal cancer patients	(n=not specified)
IBD	(n=not specified)
chronic renal failure	(n=not specified)
controls	(n=not specified)

Serum sCD44 and sCD44 (variant 6) levels were significantly elevated in most of the patient groups (medians sCD44 330-709 ng/ml, sCD44v6 125-160 ng/ml) as compared with controls (sCD44 346 ng/ml, sCD44v6 106.5 ng/ml).

**Cervical cancer** (Gadducci et al 1998)

cervical cancer patients	(n=37)
benign gynecological disease controls	(n=36)

Median serum sCD44 (standard form) levels were significantly higher ( $p=0.004$ ) in cervical cancer patients (547 ng/ml, range 244-880 ng/ml) as compared with controls (400.5 ng/ml, range 217-723 ng/ml). sCD44v5 and sCD44v6 were significantly lower in cervical cancer patients than in controls (34 ng/ml range 0-140 ng/ml vs 44 ng/ml, range 111-109 ng/ml and 37 ng/ml, range 1-191 ng/ml vs 52.5 ng/ml, range 11-173 ng/ml respectively,  $p=0.007$ ).

**Rheumatoid arthritis** (Kittl et al 1997)

patients (RA)	(n=56)
miscellaneous inflammatory rheumatic diseases (MIRD)	(n=31)

Very significantly higher ( $p<0.001$ ) levels of serum sCD44v5 were found ( $81 \pm 54$  ng/ml v  $33 \pm 13$  ng/ml) and v6 ( $237 \pm 124$  ng/ml vs  $166 \pm 53$  ng/ml) in RA patients than in those with MIRD. In RA patients elevated sCD44v5 correlated with disease activity.

**Renal cancer** (Kan et al 1996)

patients	(n=47)
healthy controls	(n=16)

Serum sCD44 was significantly ( $p=0.001$ ) elevated in patients ( $745 \pm 170$  ng/ml) as compared with healthy controls ( $563 \pm 159$  ng/ml).

**Metastatic gastric carcinoma** (Harn et al 1996)

patients with various stages of gastric carcinoma	(n=41)
normal controls	(n=10)

Levels of serum sCD44v5 ( $69.39 \pm 6.06$  vs  $25.49 \pm 1.7$  ng/ml) and sCD44v6 ( $216.62 \pm 32.98$  vs  $148.32 \pm 3.15$  ng/ml) were elevated in patients with advanced gastric carcinoma as compared with normal controls. Serum sCD44v5 correlated with the extent of tumour invasion, status of lymph node involvement and distant metastasis ( $p<0.05$ ). No further numerical data given.

**Gastrointestinal cancer** (Guo et al 1994)

advanced gastric cancer	(n=not specified)
colon cancer	(n=not specified)
normal controls	(n=not specified)

Levels of serum sCD44 were elevated in both advanced gastric cancer ( $24.2 \pm 9.8$  nM vs  $2.7 \pm 1.1$  nM in normal controls) and colon cancer ( $30.8 \pm 11$  nM vs  $2.7 \pm 1.1$  nM in normal controls).

**Pancreatic carcinoma** (Gansauge et al 1997)

pancreatic carcinoma patients (n=93)  
controls (n=not specified)

Serum sCD44 and sCD44v6 were significantly reduced in patients ( $p<0.001$  and  $p<0.00005$  respectively). The median survival in the group with sCD44v6 below 100ng/mL was significantly decreased compared with those with serum values above 100ng/mL (6.7 vs 15.1 months,  $p<0.0005$ ).

**Gastric carcinoma** (Saito et al 1998)

patients (n=102)  
controls (n=not specified)

Levels of serum sCD44 (variant 6) were significantly associated with the depth of tumour invasion, lymph node metastasis and clinical stage in patients with diffuse type gastric carcinoma. No numerical data given.

**Colorectal cancer** (Yamane et al 1999)

patients prior to surgery (n=44)  
controls (n=not specified)

Serum sCD44 (variant 6) levels were significantly ( $p<0.05$ ) associated with lymph node metastasis. The 5 year survival rate was significantly lower ( $P<0.05$ ) in patients with high (52.4%) sCD44 (variant 6). sCD44 served as prognostic indicator in these patients (no numerical data given).

**Non-Hodgkin's lymphoma** (Ristamaki et al 1998)

patients (n=123)  
controls (n=not specified)

Significantly higher levels of sCD44 were found in patients as compared with controls, and were associated with high histological grade of malignancy and poor overall survival.

**Ovarian cancer** (Zeimet et al 1997)

ovarian cancer patients (n=96)  
healthy age-matched female controls (n=50)

Serum sCD44 was found to be higher and sCD44v5 to be lower in patients than in controls. No numerical data given. A high pre-treatment serum level of sCD44v5 is associated with a favourable clinical outcome.

**Breast cancer** (Kittl et al 1997)

active metastatic breast cancer	(n=53)
recurrence of breast cancer	(n=13)
breast cancer at presentation patients	(n=85)
non-malignant breast disease controls	(n=53)
healthy controls	(n=147)

Elevated levels (>58ng/ml) of serum sCD44 were found in 50% of cases with metastatic disease, with marked elevation in 26%. In these cases sCD44v5 correlated with the extent of metastatic disease and fell during clinical response to cytoreductive therapy.

**Epithelial ovarian cancer** (Gadducci et al 1997)

patients	(n=51)
controls	(n=not specified)

Levels of serum sCD44v5 and sCD44v6 were significantly lower in FIGO stage III-IV than in stage I disease ( $p<0.0001$  and  $p=0.001$  respectively).

**Breast cancer** (Lackner et al 1998)

single organ metastasis breast cancer patients	(n=57)
multiple organ metastasis breast cancer patients	(n=not specified)
metastasis free breast cancer patients	(n=not specified)
normal controls	(n=not specified)

When metastases were detected, sCD44v5 and v6 serum levels were increased as compared to levels measured one month after tumour surgery in patients free of metastases ( $p=0.0025$  and  $p=0.0004$  respectively). In patients with single organ metastases, elevated sCD44v6 were associated with liver and bone metastasis ( $p=0.0025$ ).

**B cell chronic lymphocytic leukemia (B-CLL)** (De Rossi et al 1997)

B-CLL patients	(n=not specified)
controls	(n=not specified)

Levels of serum sCD44 are elevated in about 50% of patients. No numerical data given.

**Breast cancer** (Martin et al 1997)

node positive breast cancer patients	(n=not specified)
node negative breast cancer patients	(n=not specified)
healthy controls	(n=not specified)

Node-positive breast cancer patients had significantly elevated levels of serum sCD44v5 and v6 as compared with the two control groups ( $P<0.01$ ). No numerical data given.

**Chagas disease** (Laucella et al 1996)

patients with Chagas disease (n=56)  
controls (n=not specified)

sCD44 levels were significantly increased in the sera of patients during the acute phase of the infection. No numerical data given.

**Urological malignancies** (Lein et al 1997)

prostatic cancer patients (n=49)  
benign prostatic hyperplasia (BPH) (n=30)  
renal cell carcinoma (RCC) (n=31)  
bladder cancer (n=29)  
healthy male controls (n=30)  
healthy female controls (n=30)

Levels of serum sCD44v5 in patients with prostate cancer, BPH and RCC were significantly lower than those in the male control group ( $p<0.01$ ,  $p<0.001$ ,  $p<0.001$  respectively). No further numerical data given.

**Urological malignancies** (Lein et al 1996)

No data given.

**Chronic inflammatory bowel disease** (Polwaczny et al 1996)

No data given.

**Prostate cancer** (Jung et al 1996)

locally advanced prostate cancer (n=19)  
prostatic cancer without metastasis (n=30)  
benign prostatic hyperplasia (BPH) (n=30)  
controls (n=30)

Mean serum sCD44v5 levels were significantly lower in prostate cancer and BPH patients than in controls. No numerical data given.

**Liver disease** (Falleti et al 1997)

acute hepatitis (AH) (n=14)  
non-cirrhotic liver disease (CLD) (n=45)  
cirrhosis (C) (n=34)  
extrahepatic diseases (EHD) (n=35)  
healthy controls (HC) (n=14)

Patients with AH or C had significantly ( $p<0.01$ ) higher levels of serum sCD44 as compared with CLD, EHD and HC patients. No further numerical data given.

**sCD46 (MCP)****Systemic lupus erythematosus** (Kawano et al 1999)

active SLE	(n=not specified)
inactive SLE	(n=not specified)
RA	(n=not specified)
Primary Sjogren's syndrome	(n=not specified)
normal controls	(n=not specified)

Serum sCD46 levels were significantly ( $p=0.0003$ ) higher in active SLE ( $30.5 \pm 14.1$  ng/ml) than those in inactive SLE ( $5.8 \pm 7.1$  ng/ml), RA ( $14.9 \pm 11.6$  ng/ml,  $p=0.0218$ ), primary Sjogren's syndrome ( $12.3 \pm 11.6$  ng/ml,  $p=0.0039$ ) and normal controls ( $7.3 \pm 3.6$  ng/ml,  $p=0.0005$ ). The elevated level in active SLE patients decreased significantly ( $p=0.018$ ) to  $8.0 \pm 6.3$  ng/ml after effective therapy.

**sCD48 (Blast-1)****Lymphoid leukemias and arthritis** (Smith et al 1997)

lymphoproliferative disease (LPD) patients	(n=not specified)
arthritis patients	(n=not specified)
acute EBV infection	(n=not specified)
normal controls	(n=not specified)

Elevated levels of serum sCD48 were detected in some patients with LPD (median 41 ng/ml, range 15-48), arthritis (median = 42 ng/ml, range 13-67) and acute EBV infection (174 ng/ml) as compared with normal controls (29ng/ml, range 15-48). No further numerical data given.

**sCD50 (ICAM-3)****Systemic lupus erythematosus** (Pino-Otin et al 1995)

SLE patients (n=not specified)  
normal controls (n=not specified)

Levels of serum sCD50 were elevated in SLE patients. No numerical data given.

**Rheumatoid arthritis** (Littler et al 1997)

RA patients (n=22)  
Healthy controls (n=10)

Levels of serum sCD50 were significantly elevated ( $p=0.0327$ ) as compared with healthy controls. No numerical data given.

**Rheumatoid arthritis** (Nasonov et al 1997)

patients (n=36)  
controls (n=not specified)

Serum levels of sCD50 were elevated in 28.6% of patients. No numerical data given.

**HIV-1** (Galea et al 1997)

patients (n=not specified)  
controls (n=not specified)

Serum sCD50 levels were increased in HIV-1 patients. No numerical data given.

**Psoriasis** (Griffiths et al 1996)

psoriasis patients (n=32)  
healthy controls (n=112)

Levels of serum sCD50 were significantly elevated in patients and correlated with clinical severity. No numerical data given.

**sCD54 (ICAM 1)****Giant cell arteritis (GCA)** (Coll-Vincent et al 1999)

GCA patients	(n=64)
healthy controls	(n=35)

At the time of diagnosis GCA patients had significantly ( $p<0.001$ ) higher levels of serum sCD54 (360.55 ng/ml, SD 129.78) than controls (243.25 ng/ml, SD 47.43). Values normalized with clinical remission.

**Acute lymphoblastic leukaemia** (Hatzistilianou et al 1997)

ALL patients	(n=35)
healthy controls	(n=35)

Levels of serum sCD54 were significantly ( $p<0.001$ ) elevated in patients (646.6  $\pm$  80.9 ng/ml) as compared with normal controls (245.8  $\pm$  25.7 ng/ml). During remission following treatment, levels did not differ significantly from controls. During relapse, serum sCD54 levels were significantly ( $p<0.001$ ) higher (923.9  $\pm$  110.1 ng/ml) than those of the control group and those at the time of remission ( $p<0.001$ ).

**Metastatic hepatocellular carcinoma** (Sun et al 1999)

patients with non-metastatic HCC	(n=not specified)
patients with metastatic HCC	(n=not specified)

Serum sCD54 levels were significantly ( $p<0.05$ ) higher in HCC patients with metastasis (12.18  $\pm$  0.25) than in non-metastatic HCC patient controls (9.77  $\pm$  0.54).

**Leukemia and lymphoma** (Tacyildiz et al 1999)

child patients with leukemia or lymphoma	(n=54)
age-matched healthy child controls	(n=12)

Serum sCD54 levels were significantly higher ( $p<0.01$  in each comparison) in ALL (median value 350.9 ng/ml) or HD (286.4 ng/ml) patients as compared with controls (138.4 ng/ml). These levels significantly declined in ALL and HD patients in complete remission (185 and 145.4 ng/ml respectively,  $p<0.05$ ). High levels of serum sCD54 were associated with poor outcome and survival.

### Cervical carcinoma (Okamoto et al 1999)<sup>106</sup>

cervical cancer patients	n=not specied
patients with benign disease	n=not specified
normal controls	n=not specified

Patients with cervical cancer had significantly ( $p < 0.001$ ) higher levels ( $884.4 \pm 332.4$  ng/ml) of sCD54 than normal controls ( $364.6 \pm 134.8$  ng/ml) and patients with benign disease ( $536.3 \pm 204.8$  ng/ml).

### Bronchial asthma (El-Sawy et al 1999)

asthmatic children (mild)	(n=15)
asthmatic children (moderate)	(n=15)
asthmatic children (severe)	(n=15)
healthy controls	(n=20)

Mean serum sCD54 levels in asthmatic children were significantly higher than in controls ( $390.0 \pm 108.3$  ng/ml vs  $193.2 \pm 33.95$  ng/ml). An increase in serum sCD54 correlated well with asthma severity.

### Pre-eclampsia (Daniel et al 1999)

patients	(n=20)
controls (normotensive)	(n=20)
healthy non-pregnant women	(n=10)

Mean serum sCD54 level in patients were significantly higher than in normotensive controls ( $1831$  ng/ml  $\pm$   $534$  ng/ml vs  $1254$  ng/ml  $\pm$   $386$  ng/ml respectively,  $p < 0.05$ ).

### Graves' disease (Massart et al 1999)

patients 3,6,12,18 months following carbimazole therapy	(n=30)
patients relapsing	(n=11)
patients 2 years following therapy and in remission	(n=13)
untreated patients	(n=41)
healthy controls	(n=30)

Mean sCD54 concentration was significantly higher in untreated Graves' disease patients than in controls (mean  $\pm$  SD:  $371 \pm 108$  ng/ml vs  $243 \pm 47$  ng/ml,  $p < 0.0001$ ), until 6 months of therapy. The number of patients with sCD54 levels  $>$  mean of controls  $+2$  SD declined from 56% (23/41) at the time of diagnosis to 10% (3/29) at 18 months. At relapse, mean sCD54 levels increased compared with that at 18 months of therapy ( $288 \pm 48$  ng/ml vs  $236 \pm 59$  ng/ml,  $p = 0.005$ ).

**Advanced renal cell carcinoma** (Hobarth et al 1996)

patients	(n=16)
healthy controls	(n=20)

Compared with healthy controls, significantly ( $p < 0.01$ ) elevated baseline circulating levels of sCD54 (mean 1166 vs 230 ng/ml) were found in all patients.

**Renal cell carcinoma** (Dosquet et al 1997)

patients	n=76
healthy controls	n=41

Levels of sCD54 were significantly higher in patients with renal cell carcinoma than in controls. Levels were higher in metastatic patients (median = 687 ng/ml, range 294-1091, n=12), than in non-metastatic patients (median = 408 ng/ml, range 217-1375, n=64). No further numerical data given.

**Connective tissue disease** (Lauella et al 1999)

juvenile chronic arthritis patients (JCA)	(n=37)
Systemic lupus erythematosus patients (SLE)	(n=18)
Healthy controls	(n=25)

Mean values of sCD54 in JCA patients, SLE patients and controls were: 609 +/-184, 513 +/-139 and 210 +/-95 ng/ml respectively. These levels were significantly different (no numerical data given). In JCA patients, higher levels were found in patients with systemic disease. Levels of sCD54 were positively correlated with disease activity in SLE patients.

**Sarcoidosis** (Kim et al 1999)

patients (active disease)	(n=16)
patients (inactive disease)	(n=11)

Levels of serum sCD54 were significantly higher in patients with active disease than in those with inactive disease: 575 +/-221 ng/ml vs 263 +/- 98.5 ng/ml,  $p = 0.0001$ . In patients with active disease, levels decreased significantly following steroid therapy: 284 +/-118 ng/ml (level of significance not stated).

**Unstable angina** (Ogawa et al 1999)

unstable angina patients	(n=20)
stable exertional angina controls	(n=19)
normal controls	(n=16)

Levels of serum sCD54 were significantly ( $p < 0.01$ ) higher in unstable angina patients (217 +/-14) than in stable exertional angina (126 +/-8) and normal (120 +/- 10) controls.

**Polyarteritis nodosa** (Coll-Vinent et al 1997)

PAN patients with active disease (n=22)  
Healthy controls (n=13)

Serum sCD54 levels were significantly ( $p < 0.0001$ ) elevated in patients (488.5 +/- 201.3 ng/ml) as compared with controls. No further numerical data given.

**Inflammatory bowel disease** (Goke et al 1997)

Crohn's disease patients (n=65)  
Ulcerative colitis patients (n=28)  
Normal controls (n=58)

Serum sCD54 levels were significantly elevated in both Crohn's patients (420 +/- 19 ng/ml,  $p = 0.0001$ ) and UC patients (375 +/- 40 ng/ml,  $p = 0.0473$ ) as compared with controls (297 +/- 8 ng/ml).

**Leishmaniasis** (Schriefer et al 1995)

patients (n=not specified)  
healthy controls (n=not specified)

Serum sCD54 levels were similar in healthy controls and in patients refractory to treatment, but significantly higher in patients responsive to treatment ( $p = 0.02$ ). In refractory patients levels post-treatment were significantly higher than those pre-treatment ( $p = 0.03$ ). The pre-treatment levels of sCD54 in responders and patients refractory to antimonial therapy differed significantly ( $p = 0.02$ ) suggesting that they could be used as predictors of antimonial therapy response. No numerical data given.

**Endometriosis** (Wu et al 1998)

patients (n=36)  
controls (n=35)

Significantly increased serum sCD54 levels were found in patients with endometriosis, especially in those with advanced disease. No numerical data given.

**Head and neck cancer** (Liu et al 1999)

Nasopharyngeal carcinoma (n=30)  
Oral carcinoma (n=22)  
Laryngeal carcinoma (n=22)  
Normal controls (n=20)

Levels of serum sCD54 were significantly increased in laryngeal carcinoma patients as compared with normal controls. No numerical data given.

**Myasthenia Gravis** (Tesar et al 1998)

patients (n=20)  
controls (n=not specified)

Serum levels of sCD54 were higher in patients than in controls. Levels fell substantially following plasmapheresis therapy. No numerical data given.

**Acute stroke** (Bitsch et al 1998)

patients with completed stroke (n=26)

sCD54 levels peaked within 24hrs (P=0.04). Levels did not correlate with infarct volume or clinical disability. No further numerical data given.

**Smokers** (Bergmann et al 1998)

Serum levels of sCD54 were significantly higher in smokers than in non-smokers. No numerical data given.

**Common cold** (Becker et al 1992)

Statistically significant relationship between reduced serum sCD54 and frequency of common cold. No numerical data given.

**B-cell chronic lymphocytic leukemia** (Callea et al 1996)

advanced/progressive stage B-CLL (n=37)  
smouldering B-CLL (n=10)  
Normal controls (n=20)

Advanced/progressive stage B-CLL patients had significantly higher levels of serum sCD54 than smouldering B-CLL and normal controls. Levels directly correlated with tumour mass. No numerical data given.

**Multiple sclerosis** (Franciotta et al 1997)

Clinically active MS patients (n=16)  
Non-inflammatory neurological disease controls (n=not stated)  
Normal healthy controls (n=not stated)

Levels of serum sCD54 higher in MS patients than in controls. Levels decreased following therapy (6-methylprednisolone). No numerical data given.

**Behcet's disease** (Uchio et al 1999)

Normal controls: (n=20)  
Inactive Behcet's disease: (n=15)  
Active Behcet's disease: (n=20)

Significantly increased levels of serum sCD54 were found in the convalescent stage of the disease as compared with controls, but not in the acute stage. No numerical data given.

**NIDDM** (Gasic et al 1999)

microalbuminuric NIDDM patients (n=11)  
healthy controls (n=82)

sCD54 was significantly higher in patients ( $p < 0.001$ ) as compared with controls. No further numerical data given.

**Metastatic renal cell carcinoma** (Hoffman et al 1999)

patients (n=99)

Serum sCD54 levels  $> 360 \text{ ng/ml}$  was identified as a pre-treatment risk factor. No numerical data given.

**Rheumatoid arthritis** (Nasonov et al 1997)

patients (n=36)  
controls (n=not specified)

Serum levels of sCD54 were elevated in 74.2% of the patients. No numerical data given.

**Multiple sclerosis** (McDonnell et al 1999)

primary progressive disease (PPMS) (n=78)  
RRMS (n=71)  
SPMS (n=65)  
other neurological diseases (n=66)

Levels of serum sCD54 were significantly elevated in PPMS patients as compared with the other MS groups (vs SPMS,  $p = 0.006$ , vs RRMS in relapse,  $p = 0.0001$ , vs RRMS in remission,  $p = 0.0001$ ). No further numerical data given.

**Intermediate uveitis** (Klok et al 1999)

- (a) patients (n=61)
- (b) patients with a systemic disease: 26 sarcoid associated, 30 HLA-B27 associated (n=56)
- (c) patients without systemic disease: 30 toxoplasma chorioretinitis, 28 Fuch's (n=58)
- (d) normal controls (n=21)

Increased sCD54 levels in 34/61 patients. These levels were significantly different in groups (c) and (d), ( $p < 0.001$ ).

**Radiation pneumonitis** (Ishii et al 1999)

lung malignancy patients receiving radiotherapy (n=30)

12/30 cases developed radiation pneumonitis following radiotherapy. Serum levels of sCD54 were significantly elevated in the pneumonitis group but not in the non-pneumonitis group (data not given).

**Tuberculosis** (Behr-Perst 1999)

Increased levels of serum sCD54 were found in patients. No numerical data given.

**Diffuse Panbronchiolitis** (Mukae et al 1997)

- DPB patients (n=27)
- bronchiectasis patients (n=13)
- normal controls (n=15)

Serum levels of sCD54 were significantly elevated in DPB patients as compared with normal controls. No numerical data given.

**Multiple sclerosis** (Bilinska et al 1999)

Levels of sCD54 significantly increased in patients as compared with normal controls. No numerical data given.

**Non-Hodgkin's lymphoma** (Perez-Encinas et al 1999)

patients (n=63)

In high grade patients sCD54 levels correlated with tumour mass. No numerical data given.

**Hepatitis C** (Bagnasco et al 1998)

Hepatitis C patients (all treated with interferon)	(n=42)
Long-term responders (in remission)	(n=18)
Non-responders/relapsers	(n=24)

Basal serum levels of sCD54 were significantly higher in long-term responders than in non-responders/relapsers. Very high levels of sCD54 (>1000 ng/ml) were closely associated with long-term clinical response. No numerical data given. During treatment, levels fell significantly in the responder group.

**Metastatic breast carcinoma** (Zhang et al 1999)

patients with metastatic breast cancer (n=49)

Significantly higher serum levels of sCD54 were found in patients with liver and/or bone metastases ( $p < 0.05$ ). Mean serum sCD54 levels were significantly higher in patients with two or more metastatic sites compared with one metastatic site ( $p = 0.001$ ). No other numerical data given.

**Psoriasis** (Ameglio et al 1994)

patients	(n=14)
normal controls	(n=14)

Significant correlations were found between serum sCD54 levels and psoriasis area and severity index ( $R = 0.62$ ). No further numerical data given.

**Non-small cell lung cancer** (De vita et al 1998)

patients (n=112)

Serum concentrations of sCD54 were related to tumour burden and progression. No numerical data given.

**Schistosoma mansoni infection** (Esterre et al 1998)

Patients (n=not specified)

Levels of serum sCD54 were increased in infected individuals. Serum levels were furthermore significantly correlated with disease severity. No numerical data given.

**Ovarian cysts and tumours** (Darai et al 1998)

patients (ovarian carcinoma)	(n=11)
patients (luteal cysts)	(n=23)
patients (cystadenomas)	(n=29)
patients (dermoid cysts)	(n=9)
patients (borderline tumours)	(n=5)
normal controls	(n=not stated)

Serum levels of sCD54 were significantly higher than normal controls. No numerical data given.

**Hepatitis B** (Knolle et al 1997)

patients (with chronic hepatitis B) (n=31)

Serum sCD54 levels correlated with delta AST ( $p=0.001$ ) and delta ALT ( $p=0.002$ ).

**Hepatitis C** (Kaplanski et al 1997)

patients	(n=22)
healthy seronegative controls	(n=20)

Serum sCD54 levels were significantly elevated in patients. No numerical data given.

**Scleroderma** (Stratton et al 1998)

patients	(n=not specified)
controls	(n=not specified)

Serum sCD54 were significantly raised both in limited ( $p<0.001$ ) and diffuse ( $p<0.001$ ) scleroderma. No further numerical data given.

**Gastric cancer** (Benekli et al 1998)

Patients with previously untreated gastroadenocarcinoma	(n=27)
Healthy controls	(n=18)

Serum sCD54 levels were significantly ( $p<0.0001$ ) elevated in patients as compared with normal controls. No further numerical data given.

**HIV-1** (Galea et al 1997)

patients (n=not specified)  
controls (n=not specified)

Serum sCD54 levels were elevated in HIV-1 patients. No numerical data given.

**Sarcoidosis** (Mukae et al 1997)

Patients (n=not specified)  
Controls (n=not specified)

Serum levels of sCD54 were significantly elevated in patients as compared with controls. No numerical data given.

**Behcet's disease** (Uchio et al 1999)

patients (n=20)  
normal controls (n=20)

Patients in convalescent stage had significantly higher serum sCD54 levels than those in the acute stage (no numerical data given).

**HIV-associated Kaposi's sarcoma** (Becker et al 1997)

AIDS patients (suffering from acute infections)	(n=16)
AIDS patients (with Kaposi's sarcoma)	(n=23)
AIDS patient controls (free of active opportunistic disorders)	(n=15)
healthy HIV negative controls	(n=18)

Serum sCD54 levels were significantly ( $p < 0.005$ ) elevated in all AIDS patients, irrespective of concurrent opportunistic disorders. No numerical data given.

**sCD56** (sNCAM)**Multiple myeloma** (Kaiser et al 1996)

Multiple myeloma	(n=125)
Waldenstrom's disease	(n=20)
Monoclonal gammopathy unknown significance	(n=25)

Levels of serum sCD56 proved superior to those of serum beta-2 microglobulin and IL6 in distinguishing multiple myeloma from paraproteinemias of various causes, (specificity of 95.5%, but a low sensitivity of 40%).

**sCD58 (LFA-3)****Chronic liver disease** (Hoffman et al 1996)

chronic viral liver disease	(n=39)
autoimmune liver disease	(n=30)
alcoholic cirrhosis	(n=12)
other types of cirrhosis	(n=3)
hepatocellular carcinoma	(n=24)
normal controls	(n=61)

Serum levels of sCD58 were significantly elevated in patients with liver cirrhosis due to autoimmune liver disease ( $p<0.0001$ ) and viral liver disease ( $p=0.001$ ), but not in patients with alcoholic cirrhosis. No further numerical data given.

**Inflammatory bowel disease** (Hoffman et al 1996)

patients with Crohn's disease	(n=41)
patients with ulcerative colitis	(n=19)
normal controls	(n=24)

Serum sCD58 levels were significantly decreased in UC patients ( $p=0.025$ ) and even more so in Crohn's disease patients ( $p<0.0001$ ) as compared with normal controls. Reduction in serum sCD58 levels correlated significantly with various humoral (e.g. ESR:  $r=-0.48$ ,  $p=0.0002$ ) and clinical (e.g. CDAI:  $r=-0.44$ ,  $p=0.005$ ) parameters of disease activity.

**Rheumatoid arthritis** (Hoffmann et al 1996)

RA patients	(n=60)
Osteoarthritis patients (OA)	(n=13)
patients with psoriatic arthropathy	(n=16)
patients with spondylarthropathy (SpA)	(n=15)
normal controls	(n=61)

Serum levels of sCD58 were significantly reduced in RA patients as compared with normal controls ( $p<0.0001$ ), OA patients ( $p=0.019$ ) and SpA patients ( $p<0.0001$ ).

**Common cold** (Becker et al 1992)

Statistically significant relationship between reduced sCD58 and occurrence of common cold. No numerical data given.

**sCD62E (sELAM-1, E-selectin)****Polyarteritis nodosa** (Coll-Vinent et al 1997)

PAN patients with active disease (n=22)  
Healthy controls (n=13)

Serum sCD62E levels were significantly ( $p=0.003$ ) elevated in patients ( $60.6 \pm 27$  ng/ml) as compared with controls. No further numerical data given.

**Advanced renal cell carcinoma** (Hobarth et al 1996)

patients (n=16)  
healthy controls (n=20)

Levels of serum sCD62E were significantly ( $p<0.01$ ) elevated in all patients (70ng/ml) as compared with healthy controls (17ng/ml).

**Acute lymphoblastic leukaemia** (Hatzistilianou et al 1997)

ALL patients (n=35)  
healthy controls (n=35)

Levels of serum sCD62E were significantly ( $p<0.001$ ) elevated in patients ( $140.5 \pm 17.3$  ng/ml) as compared with normal controls ( $44.7 \pm 18.2$  ng/ml). During remission following treatment, levels did not differ significantly from controls. During relapse, serum sCD62E levels were significantly ( $p<0.001$ ) higher ( $258.2 \pm 5.1$  ng/ml) than those of the control group and those at the time of remission ( $p<0.001$ ).

**Pre-eclampsia** (Daniel et al 1998)

patients (n=20)  
normotensive controls (n=20)

The mean serum level of sCD62E was significantly ( $p<0.01$ ) higher in the pre-eclamptic group ( $61\text{ng/ml} \pm 30\text{ng/ml}$ ) than in normotensive controls ( $40\text{ng/ml} \pm 17$  ng/ml).

**Sarcoidosis** (Mukae et al 1997)

Patients (n=not specified)  
 Controls (n=not specified)

Serum levels of sCD62E were significantly elevated in patients as compared with controls. No numerical data given.

**HIV-associated Kaposi's sarcoma** (Becker et al 1997)

AIDS patients (suffering from acute infections)	(n=16)
AIDS patients (with Kaposi's sarcoma)	(n=23)
AIDS patient controls (free of active opportunistic disorders)	(n=15)
healthy HIV negative controls	(n=18)

Serum sCD62E levels were significantly decreased in the Kaposi's sarcoma group as compared to both healthy ( $p=0.0007$ ) and AIDS controls ( $p=0.04$ ). No numerical data given.

**Kawasaki disease** (Takeshita et al 1997)

Kawasaki patients	(n=16)
Henoch-Schonlein purpura	(n=6)
Healthy controls	(n=10)

Serum levels of sCD62E were significantly ( $p<0.01$ ) higher in the acute phase of Kawasaki patients than in the other groups.

**Diffuse Panbronchiolitis** (Mukae et al 1997)

DPB patients	(n=27)
bronchiectasis patients	(n=13)
normal controls	(n=15)

Serum levels of sCD62E were significantly elevated in DPB patients as compared with normal controls. No numerical data given.

**Neuroimmunological disorders** (Sakai et al 1998)

MS patients	(n=35)
Guillain-Barre syndrome patients (GBS)	(n=18)
Miller-Fisher syndrome patients (MFS)	(n=7)
Chronic inflammatory demyelinating myelopathy (CIDP)	(n=8)
Human T-lymphotropic virus type-1 associated myelopathy (HAM)	(n=25)
Controls	(n=not specified)

Serum levels of sCD62E were significantly ( $p<0.05$ ) higher in HAM patients ( $37.6 \pm 25.7$   $\mu$ g/ml) as compared with controls.

**Schistosoma mansoni infection** (Esterre et al 1998)

Patients (n=not specified)

Levels of serum sCD62E were increased in infected individuals. No numerical data given.

**Metastatic breast carcinoma** (Zhang et al 1999)

patients with metastatic breast cancer (n=49)

Significantly ( $p < 0.05$ ) higher serum levels of sCD62E were found in patients with liver and/or bone metastases.

**Acute stroke** (Bitsch et al 1998)

patients with completed stroke (n=26)

sCD62E levels decreased significantly ( $p = 0.002$ ) after 5 days. Levels did not correlate with infarct volume or clinical disability. No further numerical data given.

**Scleroderma** (Stratton et al 1998)

patients (n=not specified)  
controls (n=not specified)

Serum sCD62E levels were significantly elevated both in limited ( $p < 0.05$ ) and diffuse ( $p < 0.0001$ ) scleroderma. No further numerical data given.

**Renal cell carcinoma** (Dosquet et al 1997)

patients n=76  
healthy controls n=41

Levels of sCD62E were significantly lower in patients with renal cell carcinoma than in controls. No numerical data given.

**Head and neck cancer** (Liu et al 1999)

Nasopharyngeal carcinoma (n=30)  
Oral carcinoma (n=22)  
Laryngeal carcinoma (n=22)  
Normal controls (n=20)

Levels of serum sCD62E were significantly increased in laryngeal, oral and nasopharyngeal carcinoma. No numerical data given

**Systemic sclerosis** (Ihn et al 1998)

patients (n=80)  
healthy controls (n=20)

Serum levels of sCD62E were significantly higher in patients than in controls. No numerical data given.

**Gastric cancer** (Benekli et al 1998)

Patients with previously untreated gastroadenocarcinoma (n=27)  
Healthy controls (n=18)

Serum sCD62E levels were significantly ( $p=0.033$ ) elevated in patients with peritoneal metastasis. Elevated levels were associated with a poor prognosis. No further numerical data given.

**Graves' disease** (Hara et al 1996)

Graves' disease patients (n=not specified)  
Normal controls (n=not specified)

Serum levels of sCD62E were significantly ( $p=0.033$ ) higher in patients than in normal controls. No further numerical data given.

**Hepatitis C** (Kaplanski et al 1997)

patients (n=22)  
healthy seronegative controls (n=20)

Serum levels of sCD62E were significantly elevated in patients. No numerical data given.

**Ventilation associated pneumonia** (Froon et al 1998)

patients (n=42)

Serum levels of sCD62E increased from the day of diagnosis onwards in patients who died within 10 days of diagnosis.

**sCD62L (sL-selectin)****Neuroimmunological disorders** (Sakai et al 1998)

MS patients	(n=35)
Guillain-Barre syndrome patients (GBS)	(n=18)
Miller-Fisher syndrome patients (MFS)	(n=7)
Chronic inflammatory demyelinating myelopathy (CIDP)	(n=8)
Human T-lymphotropic virus type-1 associated myelopathy (HAM)	(n=25)
Normal controls	(n=not specified)

Serum levels of ssCD62L were significantly ( $p < 0.05$ ) higher in the active phase of the disease ( $2.20 \pm 0.6$  mg/ml) as compared with the inactive phase ( $0.6 \pm 0.25$  mg/ml) and controls ( $1.47 \pm 0.24$  mg/ml).

**Major trauma** (Muller et al 1998)

patients (with isolated moderate and severe head injuries)	(n=18)
multiple trauma patients without head injuries	(n=13)
Healthy controls	(n=22)

Serum levels of sCD62L were significantly ( $p < 0.001$ ) decreased in trauma patients upon admission ( $5.7$  pmol/ml  $\pm 1.6$ ) as compared with normal controls ( $11$  pmol/ml  $\pm 1.7$ ). In all patients, levels remained suppressed throughout then study period.

**Ulcerative colitis** (Seidelin et al 1998)

UC patients	(n=not stated)
Crohn's patients	(n=not stated)

Serum sCD62L levels were found to be significantly ( $p < 0.001$ ) elevated in UC patients but not in patients with Crohn's disease. UC patients with quiescent and severe disease activity had significantly lower ( $p < 0.005$ ) and higher ( $p < 0.002$ ) levels of sCD62L respectively. No numerical data given.

**Graves' disease** (Hara et al 1996)

Graves' disease patients	(n=not specified)
Normal controls	(n=not specified)

Serum sCD62L levels were significantly higher in patients than in normal controls, No numerical data given.

**Sarcoidosis** (Mukae et al 1997)

Patients (n=not specified)  
Controls (n=not specified)

Serum levels of sCD62L were significantly elevated in patients as compared with controls. No numerical data given.

**Autoimmune rheumatic disease** (Sfikakis et al 1999)

Rheumatoid arthritis (RA), systemic sclerosis (SSc) and SLE patients (n=75)

sCD62L levels were significantly higher in SLE patients as compared with controls. No numerical data given.

**Diffuse Panbronchiolitis** (Mukae et al 1997)

DPB patients (n=27)  
bronchiectasis patients (n=13)  
normal controls (n=15)

Serum levels of sCD62L were significantly elevated in DPB patients as compared with normal controls. No numerical data given

**Acute lymphoblastic leukemia** (Olejnik et al 1999)

ALL patients (n=30)

Serum sCD62L levels decreased significantly from the time of diagnosis to the end of intensive chemotherapy and increased at the time of relapse. No numerical data given.

**Atopic dermatitis** (Shimada et al 1999)

atopic dermatitis patients (n=70)  
contact dermatitis patients (n=18)  
psoriasis patients (n=23)  
normal controls (n=30)

Serum sCD62L levels were significantly elevated in atopic dermatitis patients as compared with normal controls. Levels correlated positively with disease severity. No numerical data given.

**sCD62P (sP-selectin)****Acute Myocardial Infarction** (Tomoda et 1998)

AMI patients (undergoing angioplasty)	(n=20)
AMI patients (undergoing TPA thrombolytic therapy)	(n=10)
Patients with stable angina pectoris (undergoing angioplasty)	(n=10)

Serum sCD62P levels were significantly ( $p<0.001$ ) elevated in AMI patients (176.6 ng/ml  $\pm$  12.9) as compared with stable angina patients (91.4 ng/ml  $\pm$  9.5). Serum sCD62P levels were significantly ( $p<0.001$ ) decreased following angioplasty in all 20 of the AMI patients (from 176.2 ng/ml  $\pm$  17.17 to 141.7 ng/ml  $\pm$  12.6). Levels increased significantly ( $p<0.005$ ) in 90% of AMI patients undergoing TPA thrombolytic therapy (from 177.4 ng/ml  $\pm$  17.2) to 248.8 ng/ml  $\pm$  17.3).

**Inflammatory bowel disease** (Goke et al 1997)

Crohn's disease patients	(n=65)
Ulcerative colitis patients	(n=28)
Normal controls	(n=58)

Serum sCD62P levels were significantly ( $p=0.0067$ ) elevated in both Crohn's patients (399  $\pm$  33 ng/ml) and UC patients (385  $\pm$  42 ng/ml,  $p=0.0193$ ) as compared with controls (251  $\pm$  33 ng/ml).

**Neuroimmunological disorders** (Sakai et al 1998)

MS patients	(n=35)
Guillain-Barre syndrome patients (GBS)	(n=18)
Miller-Fisher syndrome patients (MFS)	(n=7)
Chronic inflammatory demyelinating myelopathy (CIDP)	(n=8)
Human T-lymphotropic virus type-1 associated myelopathy (HAM)	(n=25)
Normal controls	(n=not specified)

Serum levels of sCD62P were increased in the active phase of MS (179.5  $\pm$  103.8 ng/ml), GBS (151.2  $\pm$  81.6 ng/ml), CIDP (198.6  $\pm$  81.9 ng/ml) and HAM (115.3  $\pm$  73.5 ng/ml). No further numerical data given.

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**Abdominal aortic aneurysm/peripheral arterial disease** (Blann et al 1998)

AAA patients	(n=21)
peripheral arterial disease patients	(n=42)
healthy controls	(n=42)

Serum sCD62P values were increased in AAA patients ( $p < 0.01$ ) and in peripheral arterial disease patients ( $p < 0.05$ ). No numerical data given.

**Atherosclerosis** (Blann et al 1998)

Levels of serum sCD62P were elevated in peripheral arterial disease. No other data given.

**Kawasaki disease** (Takeshita et al 1997)

Kawasaki patients	(n=16)
Henoch-Schonlein purpura	(n=6)
Healthy controls	(n=10)

Serum levels of sCD62P were significantly ( $p < 0.01$ ) higher in the subacute phase of Kawasaki patients than in the other groups.

**Graves' disease** (Hara et al 1996)

Graves' disease patients	(n=not specified)
Normal controls	(n=not specified)

Serum sCD62P levels were significantly higher in patients than in normal controls. No numerical data given.

**Diffuse Panbronchiolitis** (Mukae et al 1997)

DPB patients	(n=27)
bronchiectasis patients	(n=13)
normal controls	(n=15)

Serum levels of sCD62P were significantly elevated in DPB patients as compared with normal controls. No numerical data given.

**Autoimmune rheumatic disease** (Sfikakis et al 1999)

Rheumatoid arthritis (RA), systemic sclerosis (SSc) and SLE patients (n=75)

Serum sCD62P levels were significantly higher in RA and SSc patients as compared with controls. No numerical data given.

**Sarcoidosis** (Mukae et al 1997)

Patients (n=not specified)  
Controls (n=not specified)

Serum levels of sCD62P were significantly elevated in patients as compared with controls. No numerical data given.

**Peripheral arterial occlusive disease** (Tsakiris et al 1999)

patients (n=71)

Patients with predominantly femoropopliteal peripheral arterial occlusive disease were investigated before and after angioplasty (PTA). Serum sCD62P levels were found to be statistically significant ( $p < 0.01$  at 6 months) indicative factors for late restenosis in a logistic regression risk factor analysis, with an overall predictive value of 72%. No numerical data given.

**sCD66b** (protein not defined, but member of CEA family)**Tumour patients** (Grunert et al 1995)

kidney carcinoma patients	(n=not specified)
uterine carcinoma patients	(n=not specified)
benign tumours patients	(n=not specified)
inflammatory disease patients	(n=not specified)
healthy controls	(n=not specified)

Sensitivities of 40% have been determined for sCD66b in a high percentage of patients with uterine and kidney carcinomas. CML patients had sensitivities of 47%. No numerical data given.

**sCD66c (NCA)****Tumour patients** (Grunert et al 1995)

kidney carcinoma patients	(n=not specified)
uterine carcinoma patients	(n=not specified)
benign tumours patients	(n=not specified)
inflammatory disease patients	(n=not specified)
healthy controls	(n=not specified)

In the sera of most patients suffering from solid tumours, sensitivities for sCD66c are comparable to or lower than those for CEA. The sensitivity was much higher in early colon tumour stages. CML patients had sensitivities of 84%. No numerical data given.

**sCD66e (CEA)****Gastric cancer** (Ogoshi et al 1998)

gastric cancer patients (post-resection) (n=872)

Patients with detectable serum sCD66e who received polysacchride K (PSK) immunotherapy had a significantly ( $p=0.0136$ ) higher survival rate than those not receiving therapy. No numerical data given.

**Cancer** (Moser et al 1980)

Serum sCD66e is of value in the monitoring of cancer, as values in the serum may rise before the progression of the disease or relapse.

**Breat cancer** (Hayes et al 1994)

Serum sCD66e provides an indication of the clinical course of breast carcinoma. No further information given.

**sCD71 (Transferrin receptor)****Chronic liver disease** (Nagral et al 1999)

patients with iron deficiency anaemia (IDA)	(n=10)
patients with anaemia due to other causes	(n=16)

Median range of sCD71 in chronic liver disease patients with IDA was significantly ( $p=0.01$ ) higher (16.6 mg/ml, 11.2-24.8) than that in patients with anaemia due to other causes (6.6 mg/ml (11.2-24.8). The sensitivity of serum sCD71 levels for diagnosing iron deficiency was 91.6%, with a specificity of 84.6%.

**Chronic lymphocytic leukemia (CLL)** (Beguin et al 1993)

CLL patients	(n=42)
Normal controls	(n=31)

CLL patients had significantly ( $p<0.001$ ) increased levels of sCD71 (12,100  $\pm$  11,250 vs 5000  $\pm$  1050 ng/ml).

**Haematological malignancies** (Takubo et al 1998)

No information given.

**Chronic transfusion** (Tancabelic et al 1999)

chronically transfused patients:	(with sickle cell (SC) disease)	(n=19)
	(with thalassemia)	(n=8)

Serum sCD71 were elevated in all SS patients, even when on chronic transfusion, but were in the normal range in patients with thalassemia.

**Polycythemia** (Manteiga et al 1998)

Polycythemia vera patients	(n=22)
Patients with secondary polycythemia	(n=26)

Serum levels of sCD71 were elevated in both groups and related to iron deficiency. No numerical data given.

**Beta-thalassemia** (Gimferrer et al 1997)

Serum sCD71 levels are elevated in beta-thalassemia patients. No numerical data given.

**Aplastic anaemia and myelodystplastic syndromes** (Piedrs et al 1998)

patients with aplastic anaemia	(n=22)
patients with myelodystplastic syndromes	(n=31)
Healthy controls	(n=29)

Serum sCD71 levels were higher in treated than in untreated anaemic patients. No numerical data given.

**sCD73** (ecto-50-nucleotidase, 5'nucleotidase)**Breast cancer** (Walia et al 1995)

patients (n=25)  
normal controls (n=25)

Serum sCD73 levels was found to have a diagnostic significance for breast cancer. After mastectomy a significant decrease was found in serum levels of sCD73. No numerical data given.

**Graft-versus-host disease in bone marrow transplant recipients** (Yasmineh et al 1989)

group 1 - autologous transplant controls (n=22)  
group 2 - patients with no GVHD (n=33)  
group 3 - patients with grades 1 and 2 GVHD (n=21)  
group 4 - patients with grade 3 GVHD (n=12)  
group 5 - patients with grade 4 GVHD (n=7)

Comparison between the 5 groups showed that serum sCD73 and Alk phos were the best discriminants among all possible combinations of group pairs.

**Head and neck cancer** (Lal et al 1989)

patients (n=50)  
controls (n=not specified)

Mean serum sCD73 levels were significantly higher in patients as compared with controls. Activity was found to be increased with the advancement in the stage of the cancer. No numerical data given.

**Chronic liver and biliary disease** (Longinov et al 1989)

patients with diffuse hepatic diseases with and without cholestasis (n=86)

High serum sCD73 was found in patients with cholestasis and mechanical jaundice due to cancer of the prstatic head. A moderate rise was seen in cases of active cirrhosis without cholestasis and in choledocholithiasis.

**Liver cancer** (Tozzoli et al 1988)

patients (n=64)  
controls (n=not specified)

In primary liver cancer, the specificity of serum sCD73 was 100%. In secondary tumours it was 67%. Sensitivity was 75% and 90.5% respectively. No numerical data given.

**sCD75** (sialyltransferase)**Cancer** (Licata et al 1982)

Hyperparaathyroid patients	(n=15)
cancer patients without skeletal metastases	(n=10)

The mean serum sCD75 levels were significantly elevated ( $p < 0.005$ ) in cancer patients (21.1, range 9-46.8) as compared with hyperparathyroid patients (9.2, range 1-17.8).

**Bronchial carcinoma** (Ronquist et al 1983)

patients with malignant pulmonary disease	(n=27)
patients with benign pulmonary disease	(n=14)
patients with benign surgical diseases	(n=56)

Mean serum sCD75 levels in bronchial carcinoma group were significantly higher (583 cpm) than those in the benign surgical disease control group (428cpm). No further numerical data given.

**Alzheimer's disease** (Maguire et al 1994)

Alzheimer's disease patients	(n=not specified)
Age matched elderly controls	(n=not specified)
Young controls	(n=not specified)

Serum levels of sCD75 were significantly decreased in patients as compared with controls. No numerical data given.

**Multiple myeloma** (Cohen et al 1989)

multiple myeloma patients	(n=14)
monoclonal gammopathy (of unknown significance) patients	(n=7)
controls	(n=10)

Serum sCD75 levels were significantly elevated in multiple myeloma patients as compared with the other groups. No numerical data given.

**Brain tumours** (Shen et al 1984)

patients	(n=not specified)
normal controls	(n=not specified)

Serum sCD75 levels were significantly elevated in the pre-operative brain metastasis group.

**Multiple myeloma** (Frithz et al 1985)

untreated patients	(n=19)
treated patients	(n=13)
controls	(n=not specified)

Serum sCD75 levels were significantly elevated in patients. Levels were significantly lower in patients treated for 1-30 months with alkylating drugs and prednisolone. In untreated patients, significantly higher levels were found in those (n=11) belonging to stage III, than amongst the others (n=8) with stages I and II, suggesting a link between serum levels and tumour burden. No numerical data given.

**Hepatic disease** (Watanabe et al 1983)

No information given.

**Colon adenocarcinoma** (Griffiths et al 1982)

patients	(n=not specified)
controls	(n=not specified)

Serum sCD75 levels were elevated in patients. 86% of patients with advanced metastatic disease had abnormal levels as compared with 33% with no evidence of metastases. No numerical data given.

**Cancer** (Moser et al 1980)

Serum sCD75 is of value in the monitoring of cancer, as values in the serum may rise before the progression of the disease or relapse.

**Breast cancer** (Dao et al 1986)

No information given.

**sCD87**(urokinase receptor, uPAR, suPAR)**Colorectal cancer** (Stephens et al 1999)

pre-operative patients with colorectal cancer	(n=591)
controls	(n=not specified)

Elevated serum sCD87 levels were significantly ( $p < 0.0001$ ) associated with an increased risk of mortality. Serum sCD87 levels independently predicted survival ( $p < 0.0001$ ). No numerical data given.

**sCD95 (Apo-1, Fas)****Renal cell cancer** (Kimura et al 1999)

patients	(n=72)
healthy controls	(n=17)

21/72 patients had elevated serum sCD95 levels. Survival rates were significantly lower in the sCD95 elevated group. No numerical data given.

**Liver transplantation** (Seino et al 1999)

patients	(n=not specified)
controls	(n=not specified)

Serum sCD95 levels were significantly elevated in patients. The increase in sCD95 was positively associated with the incidence of infection, rejection and graft ischaemia. No numerical data given.

**HIV-1 infection** (Jiang et al 1997)

Patients	(n=not specified)
Controls	(n=not specified)

Serum sCD95 levels were increased in HIV-1 patients as compared with controls. No further data given.

**sCD102 (ICAM-2)****HIV-1** (Galea et al 1997)

patients (n=not specified)  
controls (n=not specified)

Serum sCD102 levels are increased in HIV-1 patients as compared with controls. Among an HIV-1 infected population, levels were higher in an asymptomatic group compared with an AIDS group. No numerical data given.

**sCD106 (VCAM-1)****Polyarteritis nodosa** (Coll-Vinent et al 1997)

PAN patients with active disease (n=22)  
Healthy controls (n=13)

Serum sCD106 levels were significantly ( $p=0.001$ ) elevated in patients ( $1176.5 \pm 514.1$  ng/ml) as compared with controls. No further numerical data given.

**Acute lymphoblastic leukaemia** (Hatzistilianou et al 1997)

ALL patients (n=35)  
healthy controls (n=35)

Levels of serum sCD106 were significantly ( $p<0.001$ ) elevated in patients ( $1786 \pm 151.8$  ng/ml) as compared with normal controls ( $798.6 \pm 78.9$  ng/ml). During remission following treatment, levels did not differ significantly from controls. During relapse, serum sE-selectin levels were significantly ( $p<0.001$ ) higher ( $2945.7 \pm 349.9$  ng/ml) than those of the control group and those at the time of remission ( $p<0.001$ ).

**Inflammatory bowel disease** (Goke et al 1997)

Crohn's disease patients (n=65)  
Ulcerative colitis patients (n=28)  
Normal controls (n=58)

Serum sCD106 levels were significantly elevated in both Crohn's patients ( $664 \pm 43$  ng/ml,  $p=0.0222$ ) and UC patients ( $963 \pm 162$  ng/ml,  $p=0.0121$ ) as compared with controls ( $510 \pm 31$  ng/ml).

**Non-insulin dependent diabetes mellitus** (Yoshizawa et al 1998). patients (n=68)

Patients with proliferative diabetic retinopathy (n=11) showed a significant ( $p=0.02$ ) increase in serum sCD106 ( $1281.8 \pm 166.3$ ) as compared with patients without signs of retinopathy ( $978.8 \pm 48.9$ ).

**Takayasu arteritis** (Noguchi et al 1998)

patients (n=73)  
normal controls (n=36)

Levels of serum sCD106 were significantly ( $p<0.01$ ) higher in patients (871.4 ng/ml) than in controls (607.9 ng/ml).

**Multiple sclerosis** (Bilinska et al 1999)

Levels of serum sCD106 were significantly increased in patients as compared with normal controls. No numerical data given.

**Non-Hodgkin's lymphoma** (Christiansen et al 1998)

NHL patients (n=116)  
healthy controls (n=31)

Levels of serum sCD106 was elevated in advanced stage disease (stages III + IV) only. Elevated levels were associated with significantly poorer disease-free ( $p=0.024$ ) and overall ( $p=0.02$ ) survival.

**HIV-associated Kaposi's sarcoma** (Becker et al 1997)

AIDS patients (suffering from acute infections)	(n=16)
AIDS patients (with Kaposi's sarcoma)	(n=23)
AIDS patient controls (free of active opportunistic disorders)	(n=15)
healthy HIV negative controls	(n=18)

Serum sCD106 levels were significantly ( $p<0.005$ ) elevated in all AIDS patients, irrespective of concurrent opportunistic disorders. No numerical data given.

**Diffuse Panbronchiolitis** (Mukae et al 1997)

DPB patients (n=27)  
bronchiectasis patients (n=13)  
normal controls (n=15)

Serum levels of sCD106 were significantly elevated in DPB patients as compared with normal controls. No numerical data given.

**Vernal keratoconjunctivitis** (Uchio et al 1999)

VKC patients	(n=30)
allergic conjunctivitis patients	(n=30)
normal controls	(n=20)

Serum sCD106 levels were significantly higher in VKC patients than in controls. No numerical data given.

**Renal cell carcinoma** (Dosquet et al 1997)

patients	n=76
healthy controls	n=41

Levels of sCD106 were significantly higher in patients with renal cell carcinoma than in controls. No numerical data given.

**Seasonal allergic rhinitis** (Masamoto et al 1999)

Serum sCD106 levels in patients were significantly higher than those in nonatopic controls. No numerical data given.

**Acute stroke** (Bitsch et al 1998)

patients with completed stroke	(n=26)
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Serum sCD106 levels reached a maximum after 5 days ( $P=0.02$ ). Levels did not correlate with infarct volume or clinical disability. No numerical data given.

**Myasthenia Gravis** (Tesar et al 1998)

patients	n=20
controls	n=not specified

Serum levels of sCD106 were higher in patients than controls (no numerical data given). Levels fell substantially following plasmapheresis therapy (no numerical data given).

**Head and neck cancer** (Liu et al 1999)

Nasopharyngeal carcinoma	(n=30)
Oral carcinoma	(n=22)
Laryngeal carcinoma	(n=22)
Normal controls	(n=20)

Levels of serum sCD106 were significantly increased in nasopharyngeal and laryngeal carcinoma. No numerical data given.

**Chronic B-lymphocytic leukaemia** (Christiansen et al 1998)

patients (n=106)

Serum levels of sCD106 reflected tumour burden more closely than any other marker. It also showed elevated levels in smouldering disease as compared with controls. Serum sCD106 levels added independent prognostic information relating to survival

**Systemic sclerosis** (Ihn et al 1998)

patients (n=80)  
healthy controls (n=20)

Serum levels of sCD106 were significantly higher in patients than in controls. No numerical data given.

**Hepatitis C** (Kaplanski et al 1997)

patients (n=22)  
healthy seronegative controls (n=20)

Serum sCD106 levels were significantly elevated in patients. No numerical data given.

**Scleroderma** (Stratton et al 1998)

patients (n=not specified)  
controls (n=not specified)

Serum sCD106 were significantly raised both in limited ( $p<0.05$ ) and diffuse ( $p<0.05$ ) scleroderma. No further numerical data given.

**HIV-1** (Galea et al 1997)

patients (n=not specified)  
controls (n=not specified)

Serum sCD106 levels were increased in HIV-1 patients. No numerical data given.

**Hodgkin's disease** (Christiansen et al 1998)

patients (n=101)  
controls (n=31)

Levels of serum sCD106 were significantly ( $p < 0.0001$ ) elevated in patients as compared with controls. Levels correlated with histology, stage, B-symptoms, and prognostic markers. No further numerical data given.

**Vernal keratoconjunctivitis** (Uchio et al 1999)

patients (n=30)  
normal controls (n=20)

Serum levels of sCD106 in patients were significantly higher than those in controls. No numerical data given.

**sCD117** (soluble c-kit)**Delayed Engraftment in Bone marrow transplantation** (Hashino et al 1997)

patients undergoing BMT (n=28)

Serum sCD117 levels in patients undergoing delayed engraftment were significantly lower than those with early engraftment. No numerical data given.

**sCD120a** (sTNFR-I)**Breast cancer** (Tesarova et al 1998)

breast cancer patients with various stages of disease (n=31)  
controls (n=not specified)

Serum levels of sCD120a were significantly ( $p < 0.001$ ) higher in patients with breast cancer (2166.6 +/- 568.9 pg/ml) than in controls (1121.3 +/- 260.6 pg/ml).

**Guillain-Barre syndrome** (Patzold et al 1998)

GBS patients (n=18)  
Multiple sclerosis patient controls (n=50)  
Healthy controls (n=not stated)

Serum sCD120a levels were significantly higher in GBS patients (1544 pg/ml SD 834) than in healthy controls (918 pg/ml SD 180) or MS patients (1064 pg/ml SD 262). No further numerical data given.

**Pre-eclampsia/eclampsia** (Williams et al 1998)

pregnant women with eclampsia (n=33)  
pregnant women with pre-eclampsia (n=138)  
pregnant women normotensive controls (n=185)

Levels of serum sCD120a were significantly ( $p < 0.001$ ) higher in women with eclampsia (1.87 ng/ml) than in controls (1.35 ng/ml). Levels were also significantly ( $p < 0.001$ ) higher in pre-eclamptic women (1.69 ng/ml) than in controls (1.35 ng/ml).

**HIV** (Sulkowski et al 1998)

patients (n=32)

Changes in serum HIV RNA were significantly associated with changes in sCD120a. No numerical data given.

**Partial liver resection** (Schroder et al 1998)

patients (n=not stated)

Uncomplicated liver resections were associated with a prolonged and significantly increased release of sCD120a until the 3rd post-operative day. No numerical data given.

**Septic shock** (Fraunbergerr et al 1998)

Patients (n=not stated)

Healthy controls (n=not stated)

Patients with septic shock had significantly elevated levels of serum sCD120a as compared with healthy controls. No numerical data given.

**Neonatal sepsis** (Doellner et al 1998)

septic patients (n=22)

non-infected neonate controls (n=127)

Both pre-term and term infected neonates had significantly ( $p<0.01$ ) higher serum levels of sCD120a. No numerical data given.

**Systemic lupus erythematosus** (Gabay et al 1997)

SLE patients (n=73)

RA patients (n=42)

SpA patients (n=18)

Levels of erum sCD120a were significantly higher in SLE patients than in the other groups. Levels correlated with disease activity. No numerical data given.

**Pancreatic cancer** (Barber et al 1999)

patients (n=13)

healthy controls (n=6)

Serum sCD120a levels were significantly higher in patients than in healthy controls. No numerical data given.

**sCD120b (sTNFR-II)****Breast cancer** (Tesarova et al 1998)

breast cancer patients with various stages of disease (n=31)  
controls (n=not specified)

Serum levels of sCD120b were significantly ( $p < 0.001$ ) higher in patients with breast cancer (3792.8 +/- 958.9 pg/ml) than in controls (1996.2 +/- 404.3 pg/ml).

**HIV** (Sulkowski et al 1998)

patients (n=32)

Changes in serum HIV RNA were significantly associated with changes in serum sCD120b. No numerical data given.

**Renal disease** (Tesar et al 1998)

patients with ANCA-A +ve renal vasculitis (AARV) (n=12)  
Patients with active lupus nephritis (LN) (n=9)  
healthy subjects (n=5)

Patients with LN and AARV had significantly elevated serum sCD120b levels as compared with controls. No numerical data given.

**Partial liver resection** (Schroder et al 1998)

patients (n=not stated)

Uncomplicated liver resections were associated with a prolonged and significantly increased release of serum sCD120b until the 5th post-operative day. No numerical data given.

**Septic shock** (Fraunbergerr et al 1998)

Patients	(n=not stated)
Healthy controls	(n=not stated)

Patients with septic shock had significantly elevated levels of serum sCD120b as compared with healthy controls. No numerical data given.

**Neonatal sepsis** (Doellner et al 1998)

septic patients	(n=22)
non-infected neonate controls	(n=127)

Both pre-term ( $p=0.01$ ) and term ( $p=0.05$ ) infected neonates had higher serum levels of sCD120b. No numerical data given.

**Atherosclerosis** (Blann et al 1998)

patients with peripheral vascular disease	(n=20)
survivors of myocardial infarction	(n=20)
healthy controls	(n=20)

Levels of sCD120b were significantly ( $p<0.01$ ) elevated in both patient groups. No numerical data given.

**Pancreatic cancer** (Barber et al 1999)

patients	(n=13)
healthy controls	(n=6)

Serum sTNFR-II levels were significantly higher in patients than in controls. No numerical data given.

**sCD122** (sIL-2Rb)

HIV (Sulkowski et al 1998)

patients (n=32)

Changes in serum HIV RNA were significantly associated with changes in sCD122. No numerical data given.

**sCD124** (sIL-4R)**Visceral Leishmaniasis** (Sang et al 1999)

Patients (n=not specified)  
Controls (n=not specified)

Patients have 8- to 10- fold more serum sCD124 than uninfected controls and patients with documented filariasis. No numerical data given.

**Plasmodium falciparum malaria** (Jakobsen et al 1996)

patients with <i>p.falciparum</i> malaria	(n=not specified)
asymptomatic <i>p.falciparum</i> controls	(n=not specified)
healthy controls	(n=not specified)

Higher levels of serum sCD124 were found in patients with malaria as compared with controls. No numerical data given.

**sCD126 (sIL-6R)****Adult T-cell leukaemia** (Horriuchi et al 1998)

ATL patients (n=12)  
 healthy controls (n=23)

Serum levels of sCD126 were significantly ( $p < 0.0001$ ) higher in ATL patients ( $28.7 \pm 20.4$  ng/ml) than in healthy controls ( $4.5 \pm 2.1$  ng/ml).

**Multiple myeloma** (Stasi et al 1998)

patients with multiple myeloma (MM) (n=164)  
 patients with monoclonal gammopathy of undetermined significance (MGUS) (n=81)  
 normal controls (n=55)

Serum sCD126 levels were significantly elevated in MM patients ( $162 \pm 134.6$  ng/ml) as compared with MGUS controls ( $58.9 \pm 36.7$  ng/ml) or normal controls ( $45.6 \pm 22.3$  ng/ml). No further numerical data given.

**Immunotherapy following bone marrow transplantation** (Toren et al 1996)

patients (who received cytokine-mediated immunotherapy) (n=15)  
 patients (who received cell-mediated immunotherapy) (n=15)  
 normal controls (n=not specified)

Serum sCD126 levels increased significantly ( $p < 0.05$ ) during cytokine-mediated immunotherapy ( $74 \pm 9$  ng/ml) as compared with pre-immunotherapy ( $46 \pm 6$  ng/ml) and post-immunotherapy ( $50 \pm 9$  ng/ml) levels. Levels were also significantly increased ( $p < 0.05$ ) following cell-mediated immunotherapy ( $87 \pm 3$  ng/ml vs  $60 \pm 2$  ng/ml).

**HTLV-1 Associated myelopathy** (Horriuchi et al 1998)

patients (n=13)  
 healthy controls (n=23)

Serum levels of sCD126 were significantly ( $p < 0.0001$ ) higher in ATL patients ( $27.5 \pm 12.1$  ng/ml) than in healthy controls ( $4.5 \pm 2.1$  ng/ml).

**Multiple myeloma** (Kyrtsolis et al 1996)

MM patients (n=80)  
normal controls (n=25)

Serum sCD126 levels were significantly ( $p<0.01$ ) elevated in patients (38 ng/ml, range 10-200) as compared with normal controls (28ng/ml, range 14-40). Median serum sIL-6R at diagnosis was significantly ( $p<0.001$ ) higher in non-responding patients (82ng/ml, range 20-200) than in responding patients (36ng/ml, range 10-120). High serum sCD126 levels correlated with poor survival.

**Severe Plasmodium Falciparum Malaria** (Wenisch et al 1999)

total number of patients with malaria (n=32)  
patients with cerebral malaria (n=8)  
patients with associated renal failure (n=10)

Serum sCD126 levels were significantly higher in the cerebral malaria and associated renal failure groups than in the others ( $p<0.01$  for both). No numerical data given.

**Bronchial asthma** (Yokoyama et al 1997)

patients with stable asthma (n=20)  
patients with a spontaneous attack of asthma (n=10)  
healthy controls (n=18)

Serum levels of sCD126 were significantly ( $p<0.05$ ) elevated in asthmatic patients (132 +/- 31 ng/ml) as compared with healthy controls (111 +/- 16 ng/ml). Levels were significantly elevated 2 and 3 days following an acute attack as compared to the stable state. No further numerical data given.

**Rheumatoid arthritis** (Kuryliszyn-Moskal et al 1998)

patients (n=80)  
healthy controls (n=30)

Serum levels of sCD126 were significantly higher in RA patients than in controls. No numerical data given.

**Neuroleptic treatment in schizophrenia** (Muller et al 1997)

schizophrenic patients (n=39)  
healthy controls (n=42)

During neuroleptic treatment there was a significant decrease in sCD126 levels. No further numerical data given.

**Major depression** (Sluzewska et al 1996)

patients (n=49)  
normal controls (n=15)

Serum sCD126 levels were significantly elevated in patients as compared with controls. No further numerical data given.

**Rheumatoid arthritis** (Robak et al 1998)

patients (n=66)  
healthy controls (n=24)

Patients with stage 3 and 4 of RA activity had significantly higher levels of serum sCD126 than controls. No numerical data given.

**Periodontitis** (Pietruska et al 1998)

patients (n=15)

Levels of serum sCD126 were significantly increased in patients. No numerical data given.

**Acute pyelonephritis** (Jacobson et al 1998)

patients (n=29)  
healthy controls (n=12)

2 weeks post-infection and following antibiotic treatment, serum sCD126 levels in patients was significantly higher than it was on admission ( $p<0.001$ ), and significantly higher than levels in controls ( $p=0.001$ ). Patients with increased levels of sCD126 at 2 weeks had significantly lower GFR at follow-up ( $p<0.05$ ). Patients infected by strains producing hemolysin had lower concentrations of sIL-6r ( $p<0.001$ ). No numerical values given.

**Plasma cell dyscrasias** (Zhao et al 1997)

patients with multiple myeloma (MM) (n=62)  
patients with macroglobulinemia (Mac) (n=5)  
patient with mu heavy chain disease (HCD) (n=1)  
healthy controls (n=15)

Serum sCD126 levels in Mac and MM stage II and III were significantly ( $p<0.01$ ) higher than those in MM stage I and healthy controls. Serum sCD126 levels were furthermore significantly ( $p<0.01$ ) higher in MM stage III as compared with stage II. No numerical data given.

**Multiple myeloma** (Wierzbowska et al 1999)

MM patients (n=67)  
healthy controls (n=24)

Serum sCD126 was detectable in 97% of patients. Levels were significantly ( $p < 0.001$ ) higher in MM patients as compared with controls. No numerical data given.

**Multiple myeloma** (Usnarska-Zubkiewicz et al 1998)

MM patients (n=36)  
healthy controls (n=not specified)

Serum sCD126 levels were significantly higher in patients than in controls. No numerical data given.

**Renal disease** (Tesar et al 1998)

patients with ANCA-A +ve renal vasculitis (AARV) (n=12)  
Patients with active lupus nephritis (LN) (n=9)  
healthy subjects (n=5)

Patients with LN and AARV had significantly elevated serum sCD126 levels as compared with controls. No numerical data given.

**Juvenile chronic arthritis** (Keul et al 1998)

patients (n=54)  
controls (n=10)

Serum sCD126 levels were significantly elevated in patients as compared with controls. No numerical data given.

**sCD137 (41-BB)****Rheumatoid arthritis** (Michel et al 1998)

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RA patients (n=12)

Healthy controls (n=12)

Serum levles of sCD137 were significantly elevated in RA patients (3.58 ng/ml, present in 12/12 patients), as compared with controls (0.18 ng/ml, present in 5/12 individuals).

**sCD141** (thrombomodulin, TM)**Respiratory distress syndrome** (Distefano et al 1998)

patients with RDS (n=18)  
controls (n=not specified)

Serum sCD141 levels were significantly ( $p < 0.05$ ) elevated in patients (276.1 ng/ml) as compared with controls (141.3 ng/ml). Levels in mechanically ventilated babies with severe RDS were significantly ( $p < 0.05$ ) higher than those with moderate RDS and treated with CPAJ (340.9 ng/ml vs 174.2 ng/ml).

**Ischaemic heart disease** (Blann et al 1997)

patients (following myocardial infarction) (n=54)  
patients from above group who experienced another MI within 49 months (n=24)

Serum sCD141 was 65 +/- 24 ng/ml in patients who suffered an end-point and 49 +/- 19 ng/ml in patients who were free of an end point ( $p = 0.009$ ).

**Coronary heart disease** (Salomaa et al 1999)

patients with coronary heart disease (n=258)  
patients with carotid atherosclerosis (n=449)  
controls (n=753)

Serum sCD141 showed a strong, graded, inverse association ( $p = 0.005$ ) with coronary heart disease. A high level of serum sCD141 may thus be associated with a decreased risk for coronary heart disease.

**Peripheral occlusive arterial disease** (Seigneur et al 1995)

patients (n=not specified)  
controls (n=not specified)

Serum levels of sCD141 were closely related both to transcutaneous oxygen pressure ( $p = 0.01$ ) and the graded clinical stages of the disease ( $p = 0.02$ ).

**Heparin therapy** (Cella et al 1997)

Exogenous heparin reduces serum sCD141 levels. No numerical data given

**Cerebral thrombosis** (Seki et al 1997)

patients with cerebral thrombosis (within 3 days of onset)	(n=28)
patients with cerebral thrombosis (more than 1 months after onset)	(n=36)
patients with cerebral thrombosis (more than 3 months after onset)	(n=6)
healthy volunteers	(n=37)

In patients with chronic phase thrombosis serum sCD141 levels were significantly higher than in controls. No numerical data given.

**sCD143 (ACE)****Sarcoidosis** (Mukae et al 1997)

Patients (n=not specified)  
Controls (n=not specified)

A significant correlation was found between serum sCD143, sICAM-1 and sVCAM-1. No numerical data given.

**sCD154 (CD40L)****Chronic lymphocytic leukaemia** (Younes et al 1998)

CLL patients	(n=51)
healthy donors	(n=55)

Serum sCD154 levels were significantly ( $p < 0.001$ ) elevated in patients (0.8 ng/ml) as compared with normal donors (0.29 ng/ml).

**sCD157 (BST-1)****Rheumatoid arthritis** (Lee et al 1996)

RA patients	(n=143)
healthy controls	(n=not specified)

In 7% of RA patients (10/143), concentrations of serum sCD157 were approximately 30 to 50 fold higher than in non-RA samples.